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THE UNIVERSITY OF ALBERTA

CARDIOVASCULAR REFLEXES DURING HIGH FREQUENCY OSCILLATORY VENTILATION

by

GEORGE REWA

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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.....
Supervisor

.....

.....

.....

DEDICATION

To my wife Oksana and

our son Oleksa

ABSTRACT

Short-term regulation of the cardiovascular system is by the cardiovascular reflexes. These may be classified as to their intra-cardiac and extra-cardiac receptor sites. A well described example of the former would be the left atrial low pressure receptors with complex unencapsulated nerve endings in the atrial endocardium and a vagal afferent nerve limb. Stimulation of these receptors results in a reflex tachycardia, mediated by the sympathetic nervous system and a reflex hypo-osmolar diuresis and naturiesis mediated both by the sympathetic nervous system and an as yet unidentified blood borne substance. An example of a high pressure vessel reflex is the carotid sinus baroreflex with mechanoreceptors located in the specialized vessel wall at the bifurcation of the common and internal carotid arteries. The afferent nerve limb is via the sinus and glossopharyngeal nerves; the reflex response to increased stimulation is a bradycardia and vasodilatation.

The reflex regulation of the pulmonary system is by the respiratory reflexes, these are classified by their physiological properties and the location of their receptors. Of the four categories of reflexes the most important are those with the slowly adapting pulmonary stretch receptors. These receptors discharge with increased lung volume in a cyclical fashion during spontaneous respiration. It has been shown by various techniques that the afferent limbs of both of the cardiovascular and pulmonary reflexes enter the same brain stem nucleus (i.e. nucleus tractus solitarius) and may radiate to the same higher centers. Interactions between the reflexes of the cardiovascular and the respiratory systems have long been postulated; a clear experimental

demonstration of an interaction in their reflex regulation has not been demonstrated. Recently, a new mode of ventilation, High Frequency Oscillatory Ventilation, has become available in which the cyclical discharge of slowly adapting stretch receptors becomes continuous.

Three series of experiments were performed:

1. Qualitative assessment of the effects of altering the parameters of high frequency ventilation on the discharge from the slowly adapting pulmonary stretch receptors.
2. Evaluation of the effects of the altered discharge from the slowly adapting pulmonary stretch receptors with respect to the reflex responses due to left atrial receptor stimualtion.
3. Evaluation of the effects of altered discharge from the slowly adapting pulmonary stretch receptors with respect to the reflex heart rate response due to isolated carotid sinus stimulation.

The findings were:

1. Alterations of two of the parameters of high frequency oscillatory ventilation, oscillatory frequency and mean airway pressure, in the model studied, altered the discharge from slowly adapting pulmonary stretch receptors.
2. The altered discharge of the slowly adapting pulmonary stretch receptors during high frequency oscillatory ventilation did not affect the cardiovascular reflexes studied.
3. During high frequency oscillatory ventilation the control heart rate was higher suggesting an increased sympathetic tone as compared to intermittent positive pressure ventilation.

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INTRODUCTION

Cardiovascular Reflexes

The maintenance of homeostasis of the cardiovascular system may be divided into short (seconds to hours) and long (days or more) term regulation. With respect to short-term regulation, the cardiovascular system is dependent on the functional integrity of the cardiovascular reflexes[1-5]. Every reflex must have an arc defined for it consisting of a receptor organ, an afferent nerve, an efferent nerve, and an effector organ. The classification and description of the cardiovascular reflexes may proceed along this outline[6]. The afferent limbs of these reflexes may be used to group the reflexes into those orginating from the heart[7] and those originating from the vessels[8]. The former may be further sub-divided into those from the low pressure chambers (atrial) and those from the high pressure chambers (ventriclar). Reflexes from the latter, the vessels, may also be sub-divided, into the baroreceptors and the chemoreceptors. In the current study the function of representative reflexes from both groups was evaluated under various physiological conditions during a new mode of artificial ventilation, high frequency oscillatory ventilation (HFOV). The intracardiac reflex studied was that due to the stimulation of the low pressure left atrial receptors while the extracardiac (vessel) reflex studied was that of heart rate change due to stimulation of the high pressure carotid sinus receptors.

These two reflexes have both been studied extensively, the left atrial receptor (LAR) reflex being the subject of a recent book[9]. A

brief review of their normal function is indicated. Cardiovascular pressure or volume receptors are mechanoreceptors that couple intravascular pressure to an electrical potential via receptor membrane distortion. The functioning of receptors on a cellular level may be explained on the basis of conventional membrane theory[10]. The cellular events are not contributory to the remainder of the discussion and with the exception of noting that drug effects, i.e. digoxin effects, can be explained on this basis[11] no further description will occur. Cardiovascular receptors may dysfunction in disease states[12] and may even contribute to maintenance of pathophysiological cardiovascular states during their abnormal functioning [13]; however, as the aim of this study was to evaluate normal physiological function, this will not form part of the current discussion. There are also numerous other cardiovascular reflex arcs that have been defined; the selection of the two arcs for the current study was based on the extent of knowledge as to their physiological function and the existence of accepted reproducable technjques for their study.

Heart rate response to left atrial receptor stimulation

Sensory nerve endings may be divided into three groups: free nerve endings, complex unencapsulated endings (e.g. Ruffini) and encapsulated endings (e.g. Pacinian corpuscles). Both of the first two types of endings exist within the heart in the atrial endocardium[14]. In the most densely innervated areas of the heart, the junctions of the superior and inferior vena cava and the right

atrium, at the junctions of the pulmonary veins and the left atrium as well as in both atrial appendages, the complex unencapsulated endings are the most common[15]. The stimulation of these receptors has been related to action potentials recorded from a strip of the cervical vagus nerve, thus defining the afferent limb of the reflex arc[16]. The physiological description of these receptors and the consequent attempt to classify them by the discharge patterns recorded from the vagus is still a matter of some controversy. Initially, two types of atrial receptors were described[17-18], Type A and Type B, the former discharging during atrial contraction in atrial systole, the 'a' wave of the atrial pressure curve; the latter during atrial filling in atrial diastole, during the 'v' wave. This classification suggests that the first type is indicative of atrial contractility while the second is indicative of atrial volume. However, other work has shown that the pattern of receptor discharge is dependent not on receptor subtype but on receptor location, such that receptors located at or near the pulmonary vein-atrial junctions, the area subject to greatest distortion with atrial contraction, were more responsive to atrial contraction, discharging in a Type A pattern, whereas those located in the lateral atrial walls or in the distal pulmonary veins would be more responsive to volume changes discharging in a Type B pattern[19]. Changing the geometry of the atria could cause interconversions among receptor subtypes rendering the original classifiction less meaningful[9]; the receptor discharge pattern can then be explained purely in terms of mechanical events. The sensitivity of a given receptor, as evaluated by its frequency of

discharge for a given stimulus, may also vary, i.e. it will decrease with prolonged stimulation, it will increase with some drugs such as digoxin[20].

The afferent nerve limb for the atrial receptor heart rate reflex is via myelinated nerve fibres which characteristically have a conduction velocity of 2-35 meters/sec as measured in the cervical vagi. Most other receptors found in the myocardium conduct via non-myelinated fibers at 1-2 meters/sec. Stimulation of such non-myelinated cardiac fibers could be responsible for the bradycardia and hypotension that some investigators have observed during atrial receptor stimulation. Not all cardiac afferent nerve traffic is via the vagus, some afferents have also been described in both myelinated and non-myelinated sympathetic nerves. The central connections of the left atrial receptor reflex will be described in a later section.

Much experimental work using different stimulation techniques has gone into delineating the afferent limb of the reflex response to the stimulation of atrial receptors. In the early 1960's a technique was developed that permitted reproducible studies of left atrial receptors. Small balloons on fine catheters were inserted into the pulmonary veins of the left lung so that the tips of the balloons lay in the pulmonary vein-atrial junctions[21], as well, another balloon could be inserted into the left atrial appendage[22]. The balloons were then distended with a small volume of warm saline, in all cases a tachycardia resulted without any significant concurrent change in systemic blood pressures (i.e. without activating the aortic arch or carotid sinus baroreceptor mechanism). The average mean increase in

heart rate with three sites stimulated (i.e. three balloons) was approximately 25 beats/min. The afferent nerve limb of the the reflex was shown to be via myelinated vagal nerve fibers; cooling these nerves in a fashion so as to block nerve traffic in myelinated fibers reversibly abolished the reflex tachycardia to left atrial receptor stimulation[16].

The efferent limb of the reflex tachycardia is solely via the sympathetic nerves to the heart. This limb may be blocked either pharmacologically with a combination of a competative beta adrenoreceptor blocking agent (e.g. propranolol) to block post-synaptic receptors and an agent to decrease nerve terminal noradrenaline release (a pre-synaptic effect) such as bretylium; or surgically by a bilateral section of the ansa subclaviae.

Other investigators using techniques similar but not identical to those described above (i.e. using larger balloons) have reported decreases in heart rate with balloon stimulation of atrial receptors[23]. This may be due to concurrent stimulation of other receptors and the vaso-depressor non-myelinated fibers. Some controversy also exists as to a possible vagal component in the efferent limbs of this reflex; however, this does not appear likely. Although the majority of the investigators have centered on left atrial receptors, it has been shown by some, but not by all investigators[24] that stimulation of right atrial sites also results in a reflex tachycardia[25].

The efferent limb of the reflex consists only of a chronotropic response[26] suggesting that the right ansa subclavia is more important than the left in the efferent limb; no ventricular inotropic response has been documented[27]. The magnitude of the reflex tachycardia to left atrial receptor stimulation can be graded by varying the number of sites in the left atrium that are stimulated (i.e. with a single pulmonary vein-atrial junction: 10.8 beats/min, with two pulmonary vein-atrial junctions: 22.2 beats/min, with three sites (two pulmonary vein-atrial junctions plus the left atrial appendage): 35.2 beats/min)[28]. Attempts to grade the amount of stimulation at a single site by varying the distending pressure have not been successful, probably for technical reasons.

The reflex response to left atrial stimulation has been found to be depressed by systemic acidemia[29], a situation that arises in a-chloralose anesthetized animals[30] unless specific measures are taken to prevent this with careful blood gas monitoring and bicarbonate administration. The site of this depression of response is felt to be on the efferent limb of the response since the effects of both right ansa subclaviae stimulation and sympathomimetic amines are reduced in acidemic animals. As well, a deep level of surgical anesthesia[31] with a chloralose or hypothermia can depress the response.

No effect on either respiration[32] nor peripheral resistance [33-34], has been documented during stimulation of left atrial receptors (some investigators have shown a peripheral vasodilatation[35] with similar but not identical techniques; again, this may be due to non-myelinated fiber receptor activation).

Thus, although some controversy still exists regarding some details of the reflex response of the left atrial receptors with respect to the cardiac effects, the majority of experimental work done is in agreement with the above described pathways. Hence the functional integrity of the reflex under different operating conditions may be studied and compared to the expected response.

Renal response to left atrial receptor stimulation

A renal efferent limb to the stimulation of left atrial receptors was first described in the mid 1950's[36] as an increase in urine flow in response to the distension of a large balloon in the left atrium so as to block the mitral orifice and raise the pressure in the left atrium[37]. The renal response has since been well defined as a hypo-osmolar diuresis and naturiesis[38]. A similar renal response may be obtained with the selective method outlined earlier for left atrial receptor stimulation, however, the largest responses are those with mitral valve obstruction. The difference in response may be attributed to the fact that the larger balloon, by raising left atrial pressure, is stimulating more receptors than the smaller balloons. With obstruction of the mitral valve not only does the left atrial pressure rise (generally by 10-20 mm Hg) but a fall in systemic blood pressure and cardiac output, as well as an accumulation of blood in the pulmonary circulation, occurs. Receptors other than those in the left atrium may be stimulated, however, the expected response for at least some of these (aortic arch and carotid sinus baroreceptors) would be the opposite of that seen and not a diuresis.

The receptor organs for this renal reflex are the same left atrial receptors[39] as for the reflex heart rate response. The afferent limb has been shown to be via myelinated vagal fibers by the same reversible cooling techniques as for the reflex tachycardia. With respect to the efferent pathway, however, the two reflexes diverge. During left atrial receptor stimualtion there is a decreased sympathetic discharge to the kidneys[40,41], which is selective for the kidneys with no change in lumbar and splenic sympathetic nerve activity[42]. This change in renal sympathetic tone may cause increases of renal blood flow and, via intra-renal pathways, affect changes in urine composition. Unlike the reflex heart rate response, however, the renal response cannot be explained solely on the basis of a change in sympathetic innervation. A number of lines of evidence have suggested that another factor is involved. Firstly, it was noted that the time course (longer activation time and longer time to return to control levels post stimulation) of the diuresis suggested changes in hormonal secretion; based on the composition of the urine alterations in antidiuretic hormone secretion were suspected. Secondly, following blockade of the sympathetic nerves with a beta blocking agent and bretylium, in a denervated kidney[43] or, in an isolated perfused kidney[44] a diuresis persisted indicating an alternate activation pathway by a blood borne agent or hormone. Volume loading of animals with a denervated heart also produced the renal response[45]. As noted above, the hormone most frequently implicated in these studies is antidiuretic hormone[46] the secretion of which was felt by most investigators to be inhibited by left atrial

receptor activation[47]. The differential response of hypothalamic neurones to osmotic stimuli and left atrial receptor stretch has also been demonstrated[48]. The possible influence of the left atrial receptors on antidiuretic hormone would not be the only such cardiovascular effect; carotid sinus stimulation can influence antidiuretic hormone secretion[49]. Not all studies are in agreement with this hypothesis, levels of antidiuretic hormone in the plasma in anesthetized dogs have been found to be higher than in the conscious animal and no reproducible significant consistent reduction (within the experimental limits of the assay) has been found. In addition, ablation of the posterior pituitary gland surgically via the sphenoid with a resultant absence of antidiuretic activity in the plasma did not result in an absence either of a diuresis in these animals[50-51] or of a reflex heart rate response[52].

That a hormone, or a blood borne diuretic substance[53], is involved in the reflex is also suggested by studies where altered secretion from insect malpighian tubules[54] was induced by plasma from dogs taken during left atrial receptor stimulation. Recent work showing granules with a diuretic substance in the left atrium[49-50] may provide the answer to the search of a blood borne diuretic substance, perhaps one that may be released from denervated hearts[45]

Thus in summary, the stimulation of left atrial receptors is known to reduce the sympathetic nervous stimulation of the kidney and cause the release of a blood borne diuretic substance, possibly antiduretic hormone, atrial granules or some other agent and induce a reflex hyposmolar diuresis and naturiesis. An experimental model in

dogs using a large balloon to obstruct the mitral valve has been developed.

Heart rate response to carotid sinus stimulation

The extracardiac receptors may be broken down into baroreceptors and chemoreceptors. The carotid sinus baroreflex is one of these high pressure extracardiac vessel reflexes active in the short-term modulation of the cardiovascular system[8,57-58]. The carotid sinus is a segmental enlargement of the internal carotid artery at its site of origin at the bifurcation of the common cartoid. Mechanoreceptors [59] are located in the adventitia of the carotid artery at this site, and increases in their stretch by distension of the artery by intravascular pressure (facilitated by a relative thining of the vessel smooth muscle content at this site) results in an increased afferent nerve activity. However, baroreceptor sites in the carotids are not limited solely to the bifurcation and may be found in other carotid segments[60].

The sensory innervation of the carotid sinus is carried in the myelinated sinus nerve branch of the glossopharyngeal nerve. The afferent discharge of these mechanoreceptors is significantly affected by alterations in the compliance or distensibility of the carotid sinus wall, i.e. from catecholamine stimulation, acidocis, hypoxemia or other factors that modify vascular smooth muscle tone. There is also an autonomic regulation of sinus distensibility via sympathetic efferent pathways that may reduce the diameter and elastic modulus of the carotid sinus[60].

The carotid sinus[61] during intraluminal non-pulsatile pressure, is stimulated at a threshold of 60 mm Hg and achieves a maximal response at 175-200 mm Hg as judged by reflex changes in heart rate and blood pressure as well as electroneurographic recordings from the sinus nerve. With pulsatile flows the reflex response of the carotid sinus is greater, at normal operating pressures, than with non-pulsatile flows. Changes in carotid sinus discharge influence cardiac function via three pathways. First, there is a direct effect on the heart with alterations in sympathetic[62] (atrial and venticular contractility, sino-atrial nodal automaticity, atrio-ventricular nodal conduction) and parasympathetic[63-64] (cardiac pacemaker, atrial contractility and atrio-ventricular nodal conduction) discharge to the heart. Secondly, the loading conditions of the heart are affected by changes in the peripheral vasomotor tone[65]. Thirdly, changes in arterial resistance will affect the afterload of the heart. Although, the afferent limb is the same, the effect of the efferent output of the left sympathetic nerves is predominantly on ventricular inotropy while that of the right sympathetic nerves is predominantly on atrial chronotropy.

In the normal animal the aortic arch baroreflex system is crucial to cardiovascular homeostasis[34]. Located in the aortic arch adventitia and at the roots of the major great vessels, these stretch receptors have classically been found to have a higher threshold (approximately 100 mm Hg) for either pulsatile or non pulsatile systems and a reduced sensitivity (as measured by the activity of the aortic nerve) to arterial pressure as compared to the carotid sinus.

The maximum aortic arch baroreceptor activity is reached with a pulsatile arterial pressure of 215 or a non pulsatile pressure of 300 mm Hg. More recent work suggests that due to a hysteresis in the response of the aortic arch receptors, they may be active at pressures lower than considered previously[66]. Although somewhat controversial, some investigators consider that, with respect to heart rate control at least, the aortic arch baroreceptors are no less important than the carotid sinus receptors.

In investigations of the great vessel reflexes it is necessary to ensure a constant level of stimulation of all the receptors except those at the site of study, which can then be varied in a controlled fashion. The study of the carotid sinus reflex heart rate responses requires either the maintenance of a constant mean systemic blood pressure, and hence an unchanged stimulus to the aortic arch baroreceptors (although variations in pulse amplitude at different control sinus pressures may result in a somewhat unequal stimulus) or a surgical denervation of the aortic arch. Due to the wide area covered by the aortic arch receptors the surgical approach is technically difficult and may be incomplete especially with respect to the bases of the right sided great vessels[67], thus the first alternative is often used.

In the current work, that of evaluating the heart rate response to changes in pressure in a vascularly isolated carotid sinus, the first technique was used. Changing the carotid sinus stimulation will change the total vascular capacity and if the intravascular volume is unchanged the blood pressure[68] thus a pressurized external reservoir

that could compensate for changes in vascular capacity and maintain a fixed mean systemic blood pressure was required. The vascularly isolated carotid bifurcation could then be stimulated by altering the distending pressure (independent of the systemic pressure) either by infusing or extracting blood. A baseline efflux of blood from the carotid sinus is maintained by small vessel wall vessels. As the sinus will reset to the prevailing pressure over 15-20 min, the range of pressures must be rapidly covered to prevent significant hysteresis[69].

Since the heart rate change due to carotid sinus pressure change in the above preparation will depend on many factors, i.e. the sinus wall compliance, the sympathetic afferent discharge to the sinus nerve terminals, etc., in order to evaluate the raw data the response must be normalized to the range of heart rates obtained and given as a percentage heart rate change per mm Hg of the carotid sinus pressure change. The curve of the function relating these two variables is sigmoid and the steep part of the curve may be taken as the characteristic response of the given preparation.

The factors that suppress the reflex response from left atrial receptors e.g. acidocis, anesthesia, etc., also suppress baroreceptor reflexes (i.e. α chloralose anesthesia can affect both the heart rate and blood pressure response[70]; in addition, other factors can affect the response, e.g. hypoxia. Chemoreceptors are located in the carotid body, situated at the bifurcation of the common carotid artery and supplied by the occipital and ascending pharyngeal arteries and the aortic bodies, located at the roots of the right and left subclavian

arteries and near the heart in the pulmonary artery and aorta (supplied by branches from the nearby systemic vessels). For studies monitoring the carotid sinus the latter are kept constant by the regulation of the arterial blood gases while the former must be surgically denervated at the time of carotid sinus catheterization since the blood perfusing the sinuses may have a low oxygen saturation. It is much more feasible to study isolated carotid sinuses rather than isolated aortic arch sinuses, for the reasons of chemoreceptor denervation, the maintenance of a constant pressure to the other receptor, (however, the carotid sinus could be denervated during aortic arch studies) and from a technical surgical viewpoint.

The reflex regulation of the cardiovascular system is a complex mechanism. The classification of reflexes given may suggest an independent function of the various reflexes; this is not so[71]. It has been found that the reflex increase in blood flow to the kidneys during left atrial receptor stimulation is modulated by input from the carotid sinus baroreceptors[72] (this may not hold for the heart rate increase limb of the left atrial receptor reflex) and during volume infusions , with presumed left atrial receptor stimulation, and a rise in arterial blood pressure, the response of the baroreceptors will diminish resulting in a tachycardia[73]. If changes in two systems, the cardiovascular and the respiratory are studied, further interactions appear[63,74]. To study individual components of this system, specific methods have been developed that attempt to isolate single reflexes so that reprodicible responses to given stimuli may be produced. If an external factor is postulated to affect the

functional integrity of the reflex regulation of the cardiovascular system, this may be evaluated by studying individual reflexes using established methods, before, during, and after the application of the external factor.

Pulmonary Reflexes

The regulation of respiration has been an area of investigation for many years[75-77] and the reflex arcs involved in this regulation have been studied for over 80 years. The reflexes are classified by their physiological properties or by the locations of their receptors. Four types of receptors, and reflexes, are defined: slowly adapting stretch receptors (SAR or Hering-Breuer receptors), rapidly adapting stretch receptors (lung irritant receptors), juxtacapillary (Type J) receptors and bronchial receptors innervated by C fibers[75] (the latter two groups are often grouped together as non-myelinated fiber receptors). The afferent limbs of the first two are by vagal myelinated fibers, the last two are by non-myelinated vagal fibers. The predominant cardiovascular effect of the non-myelinated fibers is depressor (See Introduction section on Cardiopulmonary Interactions). In addition to these airway receptors, receptors from structures outside the respiratory tract, i.e. the mediastinum, thoracic great vessels and the esophagus, show a respiratory discharge pattern[78], the role of which in the regulation of respiration is not entirely clear[79]

The slowly adapting stretch receptors are the most important group from a respiratory regulation standpoint. Thus, of the various receptors these are the most likely to have a physiological interaction with the cardiovascular system. They are involved in the regulation of inspiratory and expiratory activity (i.e. in the Hering Breuer inflation reflex, they produce apnea if the inflation stimulus is prolonged or limit the tidal volume if the ensuing deflation is restricted[80-81] and in the control of the main respiratory muscles. During spontaneous breathing with lung inflation the slowly adapting receptors show a long lasting discharge with an immediate rapid decline that slows spontaneously into a sustained discharge until deflation occurs; the main stimulus for these receptors being the trans-pulmonary pressure[77].

Slowly adapting pulmonary stretch receptors

Slowly adapting stretch receptors are unencapsulated (free ending) mechanoreceptors located in the bronchial smooth muscle, often at branching points; visualization by both light and electron microscopy has been achieved. The majority (approximately 55%[82]) are in the extrapulmonary airways with a significant proportion in the extrathoracic trachea[83]. The small airways are innervated only by

non-myelinated fibers, hence slowly adapting stretch receptors, which have myelinated fibers, are not found there. The stretch receptors are stimulated by both static and dynamic transmural pressure, thus the discharge from these receptors is dependent not only on the degree of inflation (static component) but also on the rate of inflation (dynamic component). The dynamic component is related to the viscous properties of the trachealis muscle where the receptors are located; the magnitude of both responses is dependent on bronchomotor tone[84] increasing with bronchoconstriction, decreasing with bronchodilation[85].

Slowly adapting stretch receptors can also be divided into those that are active at the end expiratory volume and those that are recruited only during inspiration[86]. The former are referred to as tonic or low threshold receptors whereas the latter are called phasic or high threshold receptors. The majority of the low threshold receptors are located in the larger extrapulmonary airways[86]. In addition to threshold characteristics, stretch receptors have been classified as to their maximum discharge characteristics. Two types of responses for lung inflation have been described, in one the discharge reaches a plateau at about 10 cm water whereas in the other there is no plateau. The former predominate in the proximal airways,

the latter in the distal airways[86]. A decreased transmural pressure (below zero) may activate extrapulmonary airway stretch receptors as well[78].

Slowly adapting stretch receptors, although mechanoreceptors in function, are variably affected by the CO_2 level in the airways[87-89]. Bronchial receptors are inhibited by increased pulmonary CO_2 [90], they are unaffected by venous or arterial CO_2. The degree of inhibition may be quite significant (up to 40% of the control discharge is inhibited by increasing the airway CO_2 from 0 to 8%[90], the effect of CO_2 is less at higher transmural pressures. The slowly adapting receptors are not oxygen sensitive and the functional significance of their inhibition by CO_2 is not yet clear, although it would serve to decrease the respiratory inhibitory influence of these receptors during ventilatory insufficiency.

In the study of slowly adapting receptor function, recordings may be taken from cervical vagus myelinated fibers (as shown by conduction velocites[91]) that show a discharge pattern that follows transmural airway pressure and its rate of change. Although the number of such fibers and receptors is not known, in the cat there are at least 1,200[92] and there is no evidence to suggest a smaller number in the dog. As mentioned previously, there are other types of vagal

and even sympathetic afferents[93] from the lung. Care must be taken in the pressures used during lung inflation so that only the slowly adapting stretch receptors are stimulated if they are the object of the experiment since stimulation of the other receptors would not be expected to produce the same responses. This same difficulty arises during the interpretation of studies of heart lung interactions where different techniques and pressures (quite often outside the physiological range) render it quite difficult to be sure that only the slowly adapting stretch receptors were activated and thus complicating the analysis.

Central Connections

Any evaluation of the reflex mechanisms involved in the homeostasis of the cardiovascular system would have to include the central connections and interconnections of these autonomic reflexes[94]. The afferent limbs of the reflex regulation of the cardiovascular and pulmonary systems, as has been outlined earlier, is via the vagus and glossopharyngeal nerves[95-96]. The majority of the fibers from these cardiopulmonary[97] and arterial mechanoreceptors[96] terminate in the nucleus of the solitary tract. From this site the information is relayed to other vasomotor centers[98], those within the reticular formation, and to the efferent nerve nuclei. As well, higher centers may be affected by input from the solitary tract, i.e., fibers pass to the hypothalamus

where they may regulate antidiuretic hormone release[48]. Routine regulation of the cardiovascular system is also modulated by the input from higher centers, i.e. the labyrinth of the inner ear via the fastigial nucleus must be connected to the vasomotor center so as to avert orthostatic hypotension. It is clear, therefore, that within the cardiovascular set of reflexes alone, numerous complex brain stem connections exist and the occurance of interactions between cardiovascular reflexes which result in a coordinated response to a stimulus is not surprising[72].

The discharge from the slowly adapting stretch receptors that corresponds to lung volume and its rate of change is also transmitted to the nucleus of the solitary tract, then to the respiratory center. That an interaction between the cardiovascular and respiratory systems may exist in the brain stem has been postulated by numerous investigators[99-100,4].

Cardiopulmonary interaction

It has long been noted that with inspiration there is an increase in heart rate; this is termed sinus arrhythmia. A number of explanations have been given to explain this phenomenon[101]: (1) a reflex stimulation of the medullary vagal efferent nucleus by increasing discharge from the slowly adapting stretch receptors (2) a direct inhibition of the vagal (cardiac efferent) nucleus by the increased discharge from the medullary respiratory center during inspiration (3) an increased discharge of the right atrial receptors

due to the increased filling of the right atrium during inspiration with a consequent sinus tachycardia. Which, if any, of these hypothesis is correct is as yet unclear, however, some experimental evidence to suggest that an interaction exists, at a central site, between the cardiovascular and respiratory system, is available. The work can be divided into four main groups: (1) neuroanatomical studies of cardiovascular and respiratory neurones including ablation and subsequent nerve degeneration and tracer migration (horseradish peroxidase or radiolabeled substances) studies to anatomically define cardiovascular and respiratory afferent tracts. (2) orthodromic (stimulation of peripheral nerve with central recording) and antidromic (stimulation of central site with peripheral nerve recording) electrophysiological stimulation studies of individual cardiovascular and respiratory neural tracts to define functional neural connections (3) brain stem recordings during experimental "physiological" (non electrical) stimulation of receptor organs to define neural connections and radiations and (4) physiological studies that demonstrate a functional interaction between the two systems. Each of these modes of investigation have their detractions, e.g., ablation studies provide only a crude localization of the structures destroyed and more may be damaged than intended with tracts other than

those of interest being destroyed; electrophysiological studies may stimulate wide areas and not only the neurones of interest, as well neuronal tracts just passing through the area without synapsing may be stimulated; technical difficulties in accurately defining the site of recording complicate brain stem recordings; and difficulties in isolating single reflex arcs and their interactions plague physiological studies.

Neuroanatomical studies consist of either tracing degenerating axons and nerve terminals after cutting the ninth and tenth cranial nerves or of destroying medullary structures and observing the effects on physiological regulation. Studies of the first type long ago demonstrated vagal projections to the nucleus of the solitary tract. Destruction of this nucleus has been shown to disrupt the reflex response to peripheral baroreceptor stimulation in the same fashion as would destruction of the peripheral receptor[102]. Absence of the reflex heart rate response to left atrial receptor stimulation following ablation of the same nucleus bilaterally has been shown[103]. Using anterograde transport of horseradish peroxidose, the projections of baroreceptor neurones have been found to have a primary synapse in the same nucleus[104]. Pulmonary afferents have also been studied using horseradish peroxidase, a connection to the

nucleus of the solitary tract was found[95]. However, with this technique, in the case of the baroreceptors, the projections of chemoreceptors cannot be separated out, and in the case of pulmonary afferents there can be no delineation as to receptor type.

Orthodromic stimulation, stimulating an entire peripheral nerve and recording centrally, has been used to study baroreceptor afferents; both for the aortic arch[105] and carotid sinus[106]. However, it may again be difficult to separate the chemoreceptor from baroreceptor fibers with this method. Single unit studies have also been done and they reinforece the finding of a central connection to the nucleus of the solitary tract from the baroreceptors.

During antidromic stimulation (central stimulation, peripheral recordings from the nerve of interest) projections to the nucleus tractus solitarius from the arotic arch[104] and the carotid sinus[107] baroreceptors have been confirmed. The exact site of insertion of nerve tracts into this area and interconnctions and projections to higher sites in the central nervous system are difficult to ascertain with this mode of study due to the large field stimulated. Since it is known that in decerebrate animals the left atrial receptor reflex is present[108] it may be postulated that any interaction between the cardiac and respiratory system should be

manifest at the brain stem level. The functional integrity of the baroreceptors requires a more extensive area of the brain stem and hypothalamus[109], perhaps providing a larger area for cardio-respiratory interactions.

Recordings from single neurones in the nucleus tractus solitarius has resulted in records of rhythmic discharges that are similar to typical baroreceptor discharges[110] as well as those that are similar to Type A and Type B atrial receptor discharges[111-113]. Another approach, that of experimental mechanical stimulation peripherally while recording centrally, has shown that balloon stimulation of left atrial receptors leads to changes in central neuronal activity[114] that can be blocked by vagal cooling[97]. Some further studies with careful neuroelectrophysiological methods indicated that nearly all neurones discharging with a cardiac rhythm show alterations in their activity related to the respiratory cycle[110]. It is possible that the respiratory modulation is indirect and via a changing peripheral cardiovascular input secondary to respiration[62] (since the cardiovascular parameters were not controlled in most of the experiments) or due to direct central respiratory center influences[63] on these neurones. However, as in animals ventilated artifically the respiratory modulation followed the ventilator

excursions and was blocked in most cases by interrupting afferent vagal nerve traffic[110], it appears that the input for this modulation to a significant extent originated in the pulmonary receptors, the most likely group being the slowly adapting stretch receptors of the lung[111] which have a typical response to lung distension. In the neurones in which there was both a cardiac and respiratory rhythm[110], it is supposed that either these were not first level neurones from the cardiovascular or respiratory receptors (which should have independent patterns so as to permit independent response to cardiovascular and respiratory reflexes) or these were first order neurones from receptors that were affected by the stimulation of both of these systems.

That physiological interactions between the cardiovascular and pulmonary systems could occur is strongly suggested by the evidence given above that document a convergence of pathways from the receptors in the two organ systems and suggest an effect of input from both systems at a single central neuronal level. However, if as mentioned earlier, a reflex is described by a receptor organ, an afferent nerve limb, a central site, an efferent nerve limb and an effector organ, then an interaction between two different reflexes should show that altered afferent input from two receptor organs results in a change in

the single efferent limb. Such a finding for a cardiovascular respiratory interaction has not yet been shown. Observations on the function of the two systems in addition to the previously described sinus arrhythmia can be evaluated either as studies during experimentally stressed physiological parameters outside the normal range or those in which the observations are obtained while the physiological parameters are in the range of normal function.

Discharges from the lungs (afferent neuronal pathway not delineated) can tonically inhibit the vasomotor center[115-117] and experimental lung inflation with high airway pressures, outside the normal range, can cause a reflex decrease in blood pressure as a result of dilatation of the systemic vessels, bradycardia and a negative inotropic effect on the ventricles[118-119]. In animals studied during intermittent positive pressure ventilation interruption of "cardiopulmonary" vagal afferents augmented the reflex vascular resposnes to changes in carotid pressure suggesting a central inhibition by the "cardiopulmonary receptors"[120] and hence an interaction of afferents from these cardiovascular and respiratory sites. In the above reports a variety of receptors was most likely stimulated. High inflation pressures of the lung were employed; these would result in stimulation of receptors other than the slowly

adapting receptors, as well, the term "cardiopulmonary" receptors covers a wide, poorly defined spectrum of thoracic receptors. At normal airway pressures the reflex response to inspiration is a tachycardia and possibly a slight vasoconstriction with the reverse seen at higher airway pressures[121]. The importance of the above is, however, that an interaction has been demonstrated to exist between the cardiovascular and respiratory systems albeit under somewhat unphysiological conditions.

At physiological airway pressures a cyclical respiratory influence on cardiovascular regulation is felt to be via slowly adapting pulmonary stretch receptors[122] with myelinated vagal nerve afferents. The contribution of the sowly adapting pulmonary stretch receptors to the tonic cardiovascular depression by lung afferents is not well elucidated, but the majority of the afferent limb appears to be via non-myelinated fibers[123]. The contributions of the slowly adapting receptors to this depression is unclear. Brief stimuli to the carotid sinus baroreceptors evoke a bradycardia only if timed during expiration, an equivalent stimulus in inspiration being ineffective. This has led to the hypothesis of respiratory gating of the baroreceptor reflex such that the cardiovascular reflex arcs are more receptive to stimuli during the expiratory portion of the

respiratory cycle. The site of this gating and the origin of the respiratory input (central, peripheral or both) are not well defined. It has also been shown that total body sympathetic discharge is altered by central respiratory center activity, being augmented with inspiration[124], and that pulmonary afferent activity exerts an important influence on the central regulation of this sympathetic discharge[125]. Although in the two studies above the effect of inspiration on sympathetic discharge was opposite (i.e. in the second it decreased sympathetic activity) this may be due to phase effects or related to the markedly different techniques used. In sum, however, sympathetic discharge tone appears to be affected by respiratory activity. As the baroreceptors reflex is influenced by the underlying sympathetic tone[61], this may be the explanation for the "gating" effect. A respiratory effect on the parasympathetic cardiac vagal efferent activity during baroreceptor reflexes has been demonstrated as well[126]. An effect of the cardiovascular reflexes on respiratory neurones has also been noted in that carotid sinus stimulation results in an increased discharge from medullary respiratory neurones[127] of uncertain significance.

The above discussion outlines that: (1) afferent neurons from the cardiovascular system, both from the systemic baroreceptors and from

the left atrial receptors, and from the pulmonary system from the pulmonary stretch receptors, synapse in the nucleus of the solitary tract (2) medullary neurones exist with both a cardiovascular and a respiratory pattern of discharge (suggesting, but not proving, that connections at this level may exist between the two systems) which may indicate a convergence between the two systems (3) afferent pulmonary nerve traffic modulates sympathetic discharge which in turn may affect cardiovascular reflex function (4) an effect of afferent pulmonary nerve traffic due to lung distension on cardiovascular responses, albeit at unphysiological pulmonary pressures, indicates that a functional interaction may exist between the two systems (5) at physiological airway pressure sinus arrhythmia, by a pathway not yet defined, links the two systems.

Until further evidence is available about a central interaction, speculation as to even higher projections and interconnections, is tentative and hence was not reviewed.

A major difficulty in evaluating the influence of lung receptors on cardiovascular reflexes has been the delineation of the changes due to respiration on the cardiovascular receptors themselves from interactions occurring in higher centers. It may be concluded that although well described reflexes with separate receptors and afferent

and efferent neurones exist in both the cardiovascular and respiratory systems and there is a geographic proximity to their central tracts, the evidence for an interaction between the two systems has not yet been conclusively established, although it appears quite likely that the respiratory system can affect the function of the cardiovascular system.

High Frequency Ventilation

The area of the effect of respiration on the function of the cardiovascular system has been an area of much investigation, as outlined previously without a clear consensus being reached. Some of the work done during intermittent positive pressure ventilation has suggested that reduced right ventricular filling[128] caused the cardiovascular changes while other studies suggested a more complex interaction[129]. Since in a normal physiological setting it may be considered that the pulmonary limb of the interrelationship between the cardiovascular and pulmonary systems would be the discharge from the slowly adapting stretch receptors, it would be useful to have a method of altering this discharge to determine its effect. As has been mentioned previously, the slowly adapting receptors may be considered to be lung volume and lung volume change receptors. Hence, during either spontaneous respiration or intermittent positive pressure ventilation there is an increase in receptor discharge during inspiration and a decrease during expiration. A technique for altering this discharge, both qualitatively and quantitatively, may be

found with high frequency ventilation.

Differences exist between various types of high frequency ventilation. Nomenclature is frequently overlapping and confusing, hence classification is best based on technical considerations and the ventilatory pattern of the three main categories of high frequency ventilation[130]. It is useful to keep intermittent positive pressure ventilation as a reference with which in dogs the respiratory rate is set at 18 breaths/min and the volume at 15 ml/kg.

The first mode of high frequency ventilation is that of high frequency positive pressure ventilation (HFPPV) which was introduced in 1967[131-132]. The major characteristics of this technique of ventilation are[133]: (1) a ventilatory frequency of 60-100 breaths/min, and an inspiration/expiratory ratio of less than 0.3 (2) a pneumatic valve to regulate gas flow (prohibiting evaluation of tidal volume due to a Venturi effect) (3) small tidal volumes (measured externally to animal) (4) positive intratracheal and negative intrapleural pressure throughout the ventilatory cycle (5) less circulatory interference than with conventional intermittent positive pressure ventilation (6) reflex suppression of spontaneous respiratory rhythmicity (7) decelerating inspiratory flow without an end-inspiratory plateau (8) more efficient pulmonary gas distribution than in conventional intermittent positive pressure ventilation. This mode of respiration has been extensively investigated, mainly in Sweden, and has been used in a variety of clinical situations, e.g. bronchoscopy, laryngoscopy etc.[134-37] with good results.

The second mode of high frequency ventilation is that of high

frequency jet ventilation(HFJV)[138-39]. With this mode of ventilation the flow of gas from a high pressure source is intermittently interrupted using a rotating valve or a solenoid so that a jet of gas may enter a catheter inserted into an endotracheal tube or percutaneously through the tracheal wall[140]; the rate is 30-240 cycles/min. As with with the previously described system, gas is entrapped by a Venturi effect at the top of the catheter so that tidal volume actually delivered to the recipient is not known. The clinical uses are similar[141-42]; it has been used in weaning patients from artificial ventilation[143].

The third mode of high frequency ventilation and the mode employed in the current study is that of high frequency oscillatory ventilation (HFOV).

High frequency oscillatory ventilation

This mode of ventilation is defined as one where the tidal volume is equal to or less than the anatomic dead space and the ventilatory frequency is between 2 and 30 Hz. Two main types of respirators are available, electromagnetic and mechanical. The former, essentially loudspeakers driven in an amplified sine-wave, are useful for small volumes at lower frequencies; at a higher value of either, the other variable decreases. Mechanical ventilators are either piston pumps (prone to rapid wear) or eccentric can rubber diaphragms (prone to sine-wave distortion at higher frequencies or volumes). A special circuit between the ventilator and the animal is then required. The connection between the ventilator and the animal is interrupted so

that a bias flow (a cross flow of fresh gas at right angles to the oscillator output) may be attached. The gas mixture and volume of flow in the bias flow input tube is controlled as is,in some systems, the output flow via the exhaust tube. A respiratory stop-cock may be placed at the top of the endotracheal tube to permit easy switching from conventional to high frequency oscillatory ventilation. As most systems differ considerably the above is a general description; a detailed description of the system used in the current study is given under "Methods". High frequency oscillatory ventilation has also been applied experimentally using presure changes in a container external to the animal with adequate gas exchange[144]. Gas exchange during conventional high frequency ventilation is dependent on oscillatory volume, oscillatory frequency, bias flow and airway pressure[145-46].

A problem with all modes of high frequency ventilation and especially high frequency oscillatory ventilation is that at the high frequencies required, the accuracy of measuring devices (which for an accurate reproduction of physiological parameters should have a frequency response of ten times the highest expected frequency[147]) is inadequate. A specific related problem with this mode of ventilation with respect to oscillatory flow is the measurement of oscillatory tidal volume[148-49]. The volume displaced by the ventilator during each respiratory cycle both in an inspiratory and expiratory motion is termed the oscillatory tidal volume, but the volume of gas moving in and out of the animal's airways (or the volume of gas moving in the gas exchanging airways) is not necessarily the same. The latter is determined by gas losses via the bias flow

mechanism and by the compliance, both of the respirator circuit and the airways of the animal. Hence, it can be significantly different from the respirator oscillatory tidal volume and the relationship between the two can change with changes in the other pump parameters. For example, histamine, an agent that causes bronchoconstriction will alter the setting of oscillatory respirator settings that provide adequate gas exchange. In order to restore gas exchange to its previous level, pump parameter settings must be altered. These interventions can both cause variable losses of gas via the exhaust tube as well as changes in stretch receptor discharge due to altered bronchial muscle tone and possibly altered ventilatory settings[150]. In the current study oscillatory tidal volume will be used to refer to the ventilator setting for this variable.

The first high frequency oscillatory ventilator was patented in 1959[151]. Experimental work was first reported in 1972[152-53] when this mode of respiration was first used in physiological research. These early experiments were complicated by hemodynamic instability (with a metabolic acidocis) of uncertain etiology[154]. More recent work has revealed a much more minor impairment of hememodynamic status [156-58] since 1980[159] when a renewed level of interest began in this mode of ventilation and many centers began to study high frequency oscillatory ventilation. A problem that has arisen in comparing the work from different centers is that due to technical differences between various respiratory circuits , comparisons are difficult to make.

Gas exchange during conventional ventilation is explained by the

bulk transport theory of fresh gas to the alveoli. During high frequency oscillatory ventilation there is no significant bulk flow; gas exchange is postulated to occur by the enchancement of diffusion[160]. In addition, the regular contraction of the heart causes localized lung oscillations which induce "cardiogenic" mixing of gases. This has been estimated to account for up to a tenfold[161] increase of gas mixing as compared to spontaneous diffusion. Strobe light studies of lungs during high frequency ventilation have shown an asynchrony of movement with phase differences evident[162] so that some regions of the lung are expanding while others are contracting, i.e. pendeluft[163] which may enchance gas mixing. Any such intra-lung gas movement may render meaningless any oscillatory tidal volume measurements taken at the level of the entire lung. Stable physiological levels of arterial blood gases may be maintained with this technique (regardless of the mechanism)[164-65]. In fact, very high flows of gas in the airways without any oscillation may maintain gas exchange at physiological levels[166].

This mode of ventilation has been employed in animals during oleic acid pulmonary oedema[146,158] without deleterious effects and in human infants with respiratory distress syndrome of the newborn[167] and in respiratory failure with improvement in respiratory and cardiovascular function. No deleterious effects on lung surfactant or lung structure have been found[168]. Indeed, since during high frequency oscillatory ventilation the airway pressure is more constant than with the large pressure swings of intermittent positive pressure ventilation, there should be less barotrauma and

less interference with lung function (e.g. lung lymph flow).

In investigations conducted during high frequency positive pressure ventilation, it was found that the afferent traffic from multi-unit slowly adapting stretch receptor recordings which were cyclical during intermittent positive pressure, became grouped and irregular during high frequency ventilation. Furthermore, efferent phrenic nerve activity decreased, indicating cessation of respiratory drive[169]. Similar work conducted during high frequency oscillatory ventilation using single unit fibers from slowly adapting stretch receptors has shown that during high frequency oscillatory ventilation the stretch receptor discharge become continuous, again the phrenic nerve activity is suppressed[170] and apnea ensues (reversible by vagal section)[171]. The frequency of discharge from slowly adapting stretch receptors at a given airway pressure is higher during high frequency oscillatory ventilation than during intermittent positive pressure ventilation, indicating a contribution from the dynamic component of the slowly adapting stretch receptors.

Since the ventilation rate during high frequency oscillatory ventilation is the highest of the rates of the three modes of high frequency ventilation, the rate of stimulation of the dynamic component of the slowly adapting stretch receptors would be the most constant and the most different from that during intermittent positive pressure or spontaneous ventilation. It is thus the best experimental approach in the technique of changing the discharge from slowly adapting stretch receptors in a qualitative and quantitative fashion. The qualitative changes are known but the quantitative

changes in the frequency of discharge from the slowly adapting stretch receptors due to alterations in the parameters of high frequency oscillatory ventilation are not known.

High frequency oscillatory ventilation thus appears to be a good technique to alter the afferent input from the slowly adapting stretch receptors if the effect of this pulmonary afferent nerve traffic on cardiovascular reflex regulation is to be investigated.

Aims of the Present Study

This study was designed to investigate the effects of qualitatively and quantitatively altered vagal nerve traffic from the slowly adapting pulmonary stretch receptors on cardiovascular reflexes. The alterations in vagal nerve traffic were achieved by the use of high frequency oscillatory ventilation.

Answers were sought to the following questions:

1. What are the quantitative changes in vagal nerve discharge from the slowly adapting pulmonary stretch receptors due to changes in the parameters of high frequency oscillatory ventilation.
2. Is the reflex response of the low pressure left atrial receptors altered during high frequency oscillatory ventilation, either with respect to the reflex tachycardia or the reflex hypo-osmolar diuresis and naturiesis.
3. Is the reflex heart rate response of the vascularly isolated carotid sinus to pressure changes altered during high frequency oscillatory ventilation.

The dog model was used since the techniques for determining cardiovascular reflexes are well established in the literature for this model.

METHODS

General

Since in this study there were four different experimental preparations used, the description in this section shall deal initally with aspects common to all preparations and then with the specific aspects of each protocol.

Mongrel dogs weighing 16-22 kg, which had been kept fasting on the morning of the experiment were used in all sections of the experiment. With the exception of five dogs in protocol IA, and the animals in protocols IB & IC (will be separately described later), which were anesthetized with pentobarbital sodium (Nembutal, Abbott Laboratories, Des Moines, Iowa) all the dogs were anesthetized with α-chloralase (Fisher Scientific, U.S.A.). The dogs were premedicated with morphine sulphate (dose 7 mg subcutaneously) then thirty minutes later they were anesthetized with an intravenous infusion of α-chloralase (dose 0.10g/kg) administered via a polyethylene catheter (I.D. 1.57 mm, Intramedic Polyethylene Tubing, Clay Adams, Parsipanny, New Jersey) introduced through the right saphenous vein to the inferior vena cava. A local anesthetic (Lidocaine, dose 10 mg xylocaine 2% w/v Astra Pharmaceutical Division, Mississauga, Ontario) was used to facilitate the insertion of this catheter. Subsequently during the experiment a steady state of light anesthesia was maintained by a continuous infusion of α chloralase as required to maintain a steady level of anesthesia (5 gm of α-chloralase in 500 ml

of normal saline [0.9% NaCl w/v], dose 0.5 to 0.75 ml/kg/10 min).

When pentobarbital sodium was used, fasting dogs were anesthetized by an initial intravenous injection (dose 25 mg/kg) and anesthesia was maintained by doses given intravenously (2.5 mg/kg) every 30-40 minutes to maintain a steady level of anesthesia.

After the induction of anesthesia the trachea was intubated with a cuffed endotracheal tube (I.D. 10 mm length 28 cm, National Catheter Co., Argyle, N.Y.) and the animal ventilated using a Harvard Respirator (Model 607, Harvard Instruments Co., Millis, Mass.) at a tidal volume of 15 ml/kg and a respiratory frequency of 18 per minute. A large bore (I.D. 7 mm) three way stop-cock was interposed between the ventilator and the endotracheal tube so as to permit the animal to be connected to either the Harvard or oscillatory ventilator. The outflow from the Harvard ventilator was placed under water to alter the end expiratory and hence mean airway pressure as required.

The high frequency ventilator used (Model VSMV Metrex Instruments Ltd., Mississauga, Ontario) had an eccentric cam mechanism driving a rubber diaphragm. The oscillatory tidal volume and oscillatory frequency settings could be adjusted on the ventilator.

The ventilator was connected to a four way connector using thick walled silastic tubing (I.D. 15 mm, Dow Corning Corporation, Midland Michigan). Two opposing ports of this four way connector were used to provide a cross (bias) flow of air enriched with oxygen (4 litres/minute, pressure 50 PSI). The gas mixture entered the connector having passed through a flow gauge (J. Nageldinger and Sons

Inc., New York N.Y.) which permitted this flow to be maintained constant. The gas leaving the connector passed through a flexible tube (I.D. 10 mm, length 210 cm., "Tygon", Johnson Industrial Plastics, Edmonton, Canada) before passing into the atmosphere. When required the tip of this tube was placed under water to alter the mean airway pressure. The fourth part of the connector was attached to the three way stop-cock which provided a means of alternately ventilating the animal by intermittent positive pressure or high frequency oscillatory ventilation (Figure 1).

The mean pressure in the trachea was measured at the level of the carina by inserting a multiple side-hole polyethylene cannula (I.D. 1.67 mm). This cannula was connected to a transducer (P23 db Gould Stratham Instruments, Hato Rey, Puerto Rico). The systemic pressure was measured through a cannula (I.D. 1.67 mm) inserted into the right femoral artery and connected to a similar transducer. The frequency response of the blood pressure recording system was found to be flat to 30 Hz (±2%). The output of both transducers was amplified and recorded on light sensitive paper (Model VR12, Electronics for Medicine/Honeywell, Pleasantville, N.Y., U.S.A.).

The esophageal temperature was monitored (Model 43TD, Yellow Springs Instrument Co. Yellow Springs, Ohio) and maintained at 37±1°C by means of heating blankets.

Arterial blood gas measurements were made at the start of each experiment and then periodically to ensure normal values (Instrumentation Laboratory Inc., pH/Blood Gas Analyzer 813, Lexington, Mass.).

Protocol I. Determinants of Slowly Adapting Stretch Receptor Discharge Frequency During High Frequency Oscillatory Ventilation.

This section of the study investigated the effect of varying the parameters of high frequency oscillatory ventilation on pulmonary stretch receptor activity.

In addition to the general procedures outlined above, the following additions were employed.

The right femoral vein was cannulated for the purpose of administering drugs and for infusions during the experiment. The animals were hydrated with a constant infusion of 5% dextrose/.9% saline (2:1) at a rate such that the total infusion rate (including α chloralose) was .1 ml/kg/min. Following this cannulation gallamine triethiodide (dose 20 mg Flaxedil, Rhone Poulenc Pharma Inc., Montreal, Quebec) was given and repeated every 45-60 minutes, as required, as a muscle relaxant.

Action potentials were recorded from afferent fibers of the cervical vagus. The left vagus was dissected away from the carotid artery and desheathed. Strips of the vagus nerve were randomly separated from the main trunk and single fiber action potentials were recorded from the peripheral end using silver electrodes. The input from the electrodes was amplified (Tektronix Type 122, Low Level Preamplifier, Tektronix Inc., Oregon) and recorded. The output from the recorder was fed into a pulse discriminator, which provided noise free tracings which were recorded along with the EKG and pressure tracings (Figure 2).

Identification of the fibers from the slowly adapting stretch

receptors was facilitated by obtaining an audio representation of the amplified action potential signal (Amplifier Model 32-2032 Radio Shack, Tandy Electronics Ltd., Barrie, Ontario).

Conduction velocity was obtained by conventional means. The vagus nerve was exposed over a length of 8 cm or more. An electrical impulse (Nerve Stimulator Model SD9B Grass Inst. Co., Quincy, Mass.) was applied 5-6 cm distal to the recording electrode. The conduction velocity was calculated from the latency of the evoked response utilizing the pulse discriminator oscilloscope and the measured exact distance between the stimulating and recording electrodes.

Three protocols were carried out in this series of experiments. In all cases, a period of stabilization was allowed to elapse following the completion of the surgical procedure. Since it was ascertained that the experimental preparation did not allow any changes in bias flow without a corresponding change in end expiratory pressure; bias flow was fixed in each section of the experiment.

In all protocols only recordings from single fiber units from slowly adapting stretch receptors were made; these were identified by their typical cyclical discharge pattern during normal airway pressures during intermitent positive pressure ventilation. Each setting was maintained for at least three minutes and recordings were taken only after the frequency of discharges from the slowly adapting stretch receptors had stabilized. Thirty second counts were obtained in duplicate or triplicate over a ninety second period and expressed as a mean value for that setting. These times were selected on the basis of previous studies which indicated that the discharge from the

slowly adatping stretch receptors had reached a steady state.

In all series control recordings of the discharge of stretch receptors during intermittent positive pressure ventilation were made before and after each period of high frequency oscillatory ventilation to establish the stability of the preparation.

Recordings were made from a variable number of pulmonary stretch receptors in each experimental animal; ranging from one to six units. As each animal has hundreds of pulmonary stretch receptors, the exact response of which to a given airway pressure will vary as the subtype and the location in the pulmonary tree, the response of one receptor is influenced very little, if at all, by its being in the same animal as another receptor. The receptor vagal units were picked randomly from the vagal nerve bundle and the results summed for all the units together. This method is an accepted experimental approach in action potential studies[172].

Protocol I A. Slowly adapting stretch receptor discharge with alterations in ventilatior settings of oscillatory tidal volume, oscillatory frequency and mean airway pressure.

In this protocol, having fixed bias flow, the other parameters of high frequency oscillatory ventilation, oscillatory tidal volume, oscillatory frequency and mean airway pressure were altered individually. Continuous recordings were obtained from single stretch receptors in strips of the cervical vagus with the animal ventilated in the following fashion (1) intermittent positive presure ventilation (2) high frequency oscillatory ventilation with the

oscillatory tidal volume setting of the pump varied to 2.5, 5.0, and 7.5 ml/kg respectively, (3) intermittent positive pressure ventilation (4) high frequency oscillatory ventilation with the oscillatory frequency setting of the pump varied to 8, 18 and 28 Hz respectively (5) intermittent positive pressure ventilation and finally (6) high frequency oscillatory ventialtion with the mean airway pressure varied to 2.1, 3.0, 6.0, 9.0 and 2.1 cm water in turn. The baseline value of 2.1 cm water was the average mean airway pressure inherent in the experimental preparation. While on high frequency oscillatory ventilation only the parameter mentioned was varied and the other pump settings were not altered. In some of these animals the conduction velocity was recorded as well.

Protocol 1 B. Slowly adapting stretch receptor discharge with individual alterations in oscillatory tidal volume, oscillatory frequency and mean airway pressure.

After the completion of the above series it became apparent that with high frequency oscillatory ventilation changes in the principal parameter (i.e. oscillatory volume, or oscillatory frequency) resulted in concurrent changes in the other determinants of ventilation (i.e. oscillatory frequency and mean airway pressure in the case of primary changes in oscillatory tidal volume and mean airway pressure in the case of primary changes in oscillatory frequency). Thus, in the second series of experiments, the dogs were studied in the same fashion as in the first except that at each setting of high frequency oscillatory ventilation only the principal parameter under

investigation was altered and the other parameters were fixed so that no absolute change occurred in them due to changes in the principal parameter. Thus, the effect of changes in only one parameter at a time was evaluated.

Protocol I C. Combined effects of oscillatory frequency and mean airway pressure on slowly adapting stretch receptor discharge.

In the third section of this experiment the individual effects and interactions of the two parameters that had been identified in protocol IB as having the greatest effect on stretch receptor discharge were investigated. These were oscillatory frequency and mean airway pressure. The other parameters, bias flow and oscillatory volume, were kept fixed in each experimental run. The oscillatory frequency was fixed at each of 8, 16 and 24 Hz in turn, then the mean airway pressure was randomly set at 3, 5, and 7 cm water.

Recordings of each stretch receptor unit during intermittent positive pressure ventilation were made before and after each change in oscillatory frequency was made.

Protocol II. Stimulation of Left Atrial Receptors During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

This section investigated the effect of altered afferent vagal nerve traffic from the stretch receptors on the reflex cardiac and renal responses to stimulation of left atrial receptors.

In addition to the general procedures outlined above the following additions were employed.

The right femoral vein was cannulated for the purpose of adminstering drugs and for infusions during the experiment. The animals were hydrated with a constant infusion of 5% dextrose/.9% saline (2:1) at a rate such that the total infusion rate (including α chloralase) was .1 ml/kg/min.

This section of the study consists of four subsections. In the first 3 subsections the reflex tachycardia to left atrial receptor stimulation was evaluated:in protocol IIA the presence of the reflex heart rate response to left atrial stimulation during high frequency oscillatory ventilation was ascertained; in IIB the heart rate response was evaluated during alterations in the respiratory parameters of high frequency oscillatory ventilation; in IIC the reflex response to graded left atrial receptor stimulation was recorded. In protocol IID the renal response to left atrial receptor stimulation during high frequency oscillatory ventilation was studied.

The surgical preparation in the first three subsections was identical, this will be described first; while the preparation in the fourth section was different and will be described separately.

In the first three sections the chest was opened in fourth intercostal space on the left and an expiratory resistance provided by placing the expiratory line under 3 cm of water. Small latex balloons (Conform Latex Tissue Finger Cots, Ackwell Industries Inc., Dothan, Alabama) on polyethylene cannulae (I.D. 1.59 mm) were placed at each of the left upper and left middle pulmonary vein-atrial junctions and a larger latex balloon (digit of surgical glove Roll-proof sheers, Ingram & Bell Ltd, Don Mills, Ontario) on a similar cannula was

inserted into the left atrial appendage. A polyethylene cannula (I.D. 1.67 mm) with a side hole was inserted into the left atrium to record pressures. Following this cannulation the upper and middle lobes of the left lung were tied off. The left atrial appendage and pulmonary vein-atrial junctions were stretched by distending the balloons with warm saline, the appendage with approximately 3-4 ml, the vein-atrial junctions with approximately 1.0-1.5 ml.(Figure 3).

In some of the animals in the second section the pressure in the inferior vena cava was also recorded using a multiple side hole polyethylene (I.D. 1.77 mm) cannula inserted through the right femoral vein.

In the fourth section the chest was opened in the same fashion. A single large latex balloon on a cannula was placed in the left atrium. A polyethylene cannula (I.D. 1.67 mm) with a side hole was inserted into the left atrium to record pressure. Through a midline abdominal incision the ureters were disected free and polyethylene cannulae (I.D. 1.19 mm) with side holes were inserted and the distal ureters were tied off. The distal ends of the cannulae were then placed in calibrated test tubes so that the urine output could be measured. The atrial receptors were stimulated by distending the large balloon so as to block the mitral orifice and raise the pressure in the left atrium by approximately 10 cm water.(Figure 4)

Four subprotocols were carried out in this series of experiments. In each case a period of at least 30 minutes, for stabilization, post surgery, was allowed to elapse. As in the previous section bias flow was fixed in each section of the

experiment.

Protocol IIA. Left atrial receptor heart rate reflex during intermittent positive pressure and high frequency oscillatory ventilation.

The first protocol studied whether the reflex rise in heart rate present during intermittent positive pressure ventilation was still present during high frequency oscillatory ventilation. Intermittent positive pressure ventilation, as opposed to spontaneous respiration, was required in the control periods due to the use of surgical anesthesia.

Stimulations were done first during intermittent positive pressure ventilation (IPPV) then during high frequency oscillatory ventilation, then again during intermittent positive pressure ventilation, each sequence repeated twice. Finally, the right and left ansae subclaviae were crushed and a final sequence completed. During each stimulation sequence, at least two minutes were recorded as an initial control period. The recording was continued as the stimulus was applied for two minutes. Then the stimulus was removed and a further recording obtained for five minutes or until the heart rate stabilized.

For the purpose of analyzing the data the heart rate was counted over the final minute of each period. The control value was taken to be the average of the two control periods. This value was compared with the value obtained during the period of stimulation for both the heart rate and for the other physiological parameters.

Protocol IIB. Left atrial receptor heart rate reflex with variable slowly adapting receptor discharge frequencies (during high frequency oscillatory ventilation).

In this protocol the effect on the reflex tachycardia due to left atrial receptor stimulation was studied at various settings of the high frequency oscillatory ventilator parameters. Work from Protocol IA had shown that changing the pump parameter settings of oscillatory tidal volume and oscillatory frequency would result in a predictable change in slowly adapting receptor discharge.

Following a similar protocol for the stimulations the following sequence was carried out: (1) during intermittent positive pressure ventilation (2) during high frequency oscillatory ventilation with the oscillatory tidal volume nominally fixed at 5 ml/kg and oscillatory frequencies of 8, 16 and 25 Hz in turn (3) during intermittent positive pressure ventilation (4) during high frequency oscillatory ventilation with the oscillatory frequency fixed at 16 Hz and volumes of 2.5, 5.0 and 7.5 ml/kg in turn (5) during intermittent positive pressure ventilation.

Protocol II C. Left atrial heart rate reflex with graded left atrial receptor stimulation during intermittent positive pressure and high frequency oscillatory ventilation.

In this protocol the effect of grading the left atrial receptor stimulation by varying the number of sites stimulated was studied.

Following a similar protocol for the stimulation the following sequence was carried out: (1) during intermittent positive pressure

ventilation with all three balloons (one each on the upper and middle left pulmonary vein-atrial junctions and one in the left atrial appendage) inflated (2) during intermittent positive pressure ventilation with only the two pulmonary vein-atrial junction balloons inflated (3) during intermittent positive pressure ventilation with only one of the pulmonary vein-atrial junction balloons inflated (4,5,6,) repetition of the above sequences during high frequency oscillatory ventilation(7,8,9), repetition of the initial sequences on intermittent positive pressure ventilation. The high frequency ventilation parameters were an oscillatory tidal volume of 5 ml/kg and a frequency of 16 Hz.

Protocol II D. Left atrial receptor renal reflex during intermittent positive pressure and high frequency oscillatory ventilation.

In this protocol the renal response to left atrial receptor stimulation was evaluated.

Following a similar period of stabilization post surgery, sequential ten minute urine collections were obtained until three consecutive ones had stabilized to ±1 ml. These were taken as the control period. The mitral valve was then obstructed by distending the left atrial balloon for thirty minutes and then deflating it. During the period of stimulation and for forty mintues post stimulation the urine collections were continued every ten minutes. The volume of urine was recorded and the sample then sent for electolyte (sodium) and osmolality measurement (Corning Flame Photometer, Model 430, Corning EEL, Evans Electroselenium Ltd.,

Halstead, England and Osmette S., Model N.4002, Precision Systems, Waltham, Mass., U.S.A). In all cases the data for the three initial control periods, the last two periods during stimulation and the first post stimulation and the last three periods were averaged to provide the control, the stimulation and the control values. In alternate animals the sequence of testing was intermittent positive pressure ventilation then high frequency oscillatory ventilation, then again intermittent positive pressure ventilation and the reverse sequence. The high frequency ventilation parameters were an oscillatory tidal volume of 5 ml/kg and a frequency of 16 Hz.

Protocol III. Isolated Carotoid Sinus Reflex Heart Rate Response During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

This section investigated the effect of altered afferent vagal nerve traffic from the slowly adapting stretch receptors on the heart rate response to alteration in pressure in vascularly isolated carotid sinuses (systemic blood pressure fixed).

In addition to the general procedures outlined previously the following additions were employed. The right femoral vein was cannulated for the purpose of administering drugs and for infusions during the experiment. The animals were hydrated with a constant infusion of .9% saline w/v at as slow a rate as possible.

The dogs were given 2,000 iu of heparin sulphate i.v. (Allen and Hanburys, Galaxo Canada Toronto) and one million units of crystalline penicillin (Crystapen, Galaxo Laboratories, Toronto, Ontario). A

tapered cannula (16F, Bardic) was introduced into the left femoral artery and positioned so that the tip lay at the bifurcation of the abdominal aorta. The distal end of this cannula was connected (240 mm I.D. 3/16 inch Nalgene 8000 Tubing) to an arterial reservoir (clear plastic cylinder 340 mm in height, 150 mm in diameter, volume 6.5L) which had been primed with 500 ml of Dextran 40 in dextrose 5% (Rheomacrodex 10% w/v, Pharmacia (Canada) Ltd., Dorval, Quebec) to which had been added 1,000 iu of heparin. The pressure in the sealed arterial reservoir was maintained constant by varying the balance between (a) the inflow of pressurized air and (b) loss of pressure via an adjustable stop-cock (Propper, West Germany). A water heater (Hoake, Gebruder, Type F.E., Berlin, West Germany) connected to a coil in the arterial reservoir maintained the blood at 37±1.0°C.

The cervical carotid arteries at the level of the carotid bifurcation were carefully disected out and a metal "u" shaped cannula (depth of "u" 3 cm, spread of tips of "u" 5 cm, I.D. 3 mm) with a side arm (length 1.7 mm, I.D. 1 mm), to which a pressure transducer (model P23 db Gould Stratham Instruments) was attached via a polyethylene cannula, (I.D. 1.67 mm) was inserted. A second side arm of the "u" shaped cannula (length 40 mm, I.D. 5 mm) was connected via an intravenous infusion set (Softset i.v. set, Cutter (Canada) Ltd., Calgary, Alberta), through a pressurized air traping chamber (clear plastic cylinder 230 mm x 25 mm, volume 120 cc) to the arterial reservoir. A roller pump (Mini Puls 2 Gibson Medical Electronics, France) was placed between the arterial reservoir and the air trapping chamber to permit variable rates of perfusion of the carotid

sinuses. The reservoir and air trapping chambers were connected (Nalgene 8000 tubing). The internal and external carotids, the occipital arteries as well as any other visible arteries were then bilaterally ligated; care was taken to inactivate the carotid bodies by ligating the occipital arteries at their origins. Blood from the isolated sinus was allowed to flow away through small lateral muscular branches. A third chamber (clear plastic cylinder 205 mm in height, 50 min in diameter, volume 400 ml non-pressurized) was connected (Nalgene 8000) via the same roller pump in a reverse direction to the carotid sinus perfusion circuit so that the volume in the arterial reservoir could be held constant (Figure 5).

With the above arrangement the pressure in the carotid sinuses could be varied independently of the systemic pressure by adjusting the settings on the roller pump and the pressure generated in the carotid sinuses measured. The systemic arterial pressure was kept fixed by maintaining a constant air presure above the blood in the arterial reservoir; the volume of blood in the reservoir was permitted to change in response to compliance changes in the cardiovascular system.

At the completion of the surgical protocol the animal was permitted to stabilize. The systemic blood presure was fixed at 110 to 125 mm Hg and the carotid sinus pressure was regulated to 120 mm Hg and then raised in 20 mm Hg increments until either no further change in heart rate was obtained or no further carotid sinus pressure increment was possible. The carotid sinus pressure was then dropped to 100 mm Hg and decreased by 20 mm Hg decreases until no further

change in heart rate occurred. The carotid sinus pressure was then returned to 120 mm Hg for a final control. The above protocol was initially done during intermittent positive pressure ventilation, then repeated during high frequency oscillatory ventilation and then repeated again during intermitttent positive pressure ventilation. At each level of carotid sinus pressure, the recordings were obtained over a minute, only when all the variables were stable. The pressure at each setting was maintained for as short a period as possible to prevent resetting of the carotid sinus.

STATISTICAL ANALYSIS

General

The data is given as the arithmetic mean plus or minus the standard error of the mean.

In all cases significance was taken at $p<0.05$. Where two or more treatments were compared by an analysis of variance (ANOVA) the least significant difference test (LSD) at $p<0.05$ was used if the ANOVA was significant.

Protocol I, Determinants of Slowly Adapting Stretch Receptor Discharge Frequency During High Frequency Oscillatory Ventilation.

In protocol IA and IB a two way analysis of variance was used; in protocol IC a split plot analysis of variance was used. Due to the wide range of discharge frequencies the data in protocol IA and IB were also evaluated by the non-parametric Wilcoxan test. In the first protocol where a number of parameters changed simultaneously, an analysis of covariance was used to assist in delineating the primary parameter effect apart from the effect of concurrent change in mean airway pressure.

In all experiments, the frequencies of discharge from stretch receptors during intermittent positive pressure ventilation before, during, and after the experimental protocol on high frequency oscillatory ventilation were evaluated by a two way analysis of variance to determine if the experimental preparation had remained stable over the course of the study.

Protocol II. Stimulation of Left Atrial Receptors During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation

In protocols II A, B, and C the paired student-t test was used to determine if the heart rate change with a given set of respiratory parameters was significant during stimulation as compared to control.

In protocol IIA the student-t test was also used to determine if the other physiological parameters changed during the period of stimulation. As an alternative method of evaluating the responses the heart rate increased during stimulation during intermittent positive pressure ventilation for each sequence were averaged and then compared to the increase during high frequency oscillatory oscillation on that run.

In protocol IIB the two way analysis of variance was used to compare the heart rate responses, as well as the other physiological parameters, at the various settings of the respiratory parameters. The responses during intermittent positive pressure ventilation between the sequences during high frequency ventilation were evaluated by a two way analysis of variance.

In protocol IIC the two way analysis of variance was used to compare the heart rate responses at the various grades of left atrial receptor stimulation as well as the other physiological parameters for both modes of ventilation.

In protocol IID the data were analyzed by the paired student-t test for urine flow, urine sodium, total sodium excretion and osmolality. No evaluation statistically was done of the left atrial pressure, heart rate and blood pressure since the technique employed called for a significant obstruction at the mitral valve (to raise left atrial

presure) intentionally causing a drop in blood pressure and a resultant tachycardia.

Protocol III. Isolated Carotid Sinus reflex Heart Rate Response During Intermittent Positive presure and High Frequency Oscillatory Ventilation.

The range of heart rates in each experimental run was normalized to a range of 0 to 100 and the arithmetic mean of the normalized heart rates in the carotid sinus pressure ranges of 45-64, 65-84, 85-104, 105-124, 125-144, 145-164, 165-184, 185-204, 205-224 mm Hg were plotted against the midpoints of these carotid sinus pressure ranges, namely 55, 75, 95, 115, 135, 155, 75, 195, and 215 mm Hg respectively. This resulted in a plot of normalized heart rate as a function of carotid sinus pressure. For each run the data for the initial and final controls on intermittent positive pressure ventilation were taken together. The data below the range of 85-104 mm Hg carotid sinus pressure showed a leveling off of the heart rate response and were not included in the subsequent regression analysis. The linear regression equation for the pressure range 85-224 was then determined by the method of least squares difference for both modes of ventilation (for each experimetnal run). The two sets of slopes (percent heart rate changes per mm Hg change in carotid sinus pressure) were compared using the student-t test. The values for normalized heart rates with each mode of ventilation at the various carotid sinus presures and the other physiological parameters were compared using the two way analysis of variance.

RESULTS

Protocol I. Determinants of Slowly Adapting Stretch Receptor Discharge Frequency During High Frequency Oscillatory Ventilation.

Protocol IA. Slowly adapting stretch receptor discharge with alterations in ventilator settings of oscillatory tidal volume, oscillatory frequency, and mean airway pressure.

In the 10 experimental animals studied the heart rate and mean arterial pressure at the commencement of the protocol during intermittent positive pressure ventilation were 126.4±18.3 beats/min and 113.9±7.8 mmHg. The arterial pH, PCO_2 and PO_2 were 7.39±0.02, 37.4±1.7 mm Hg and 240±23 mm Hg respectively. The frequencies of discharge from slowly adapting receptors obtained during control periods during intermittent positive pressure ventilation were 24.2±3.7 25.5±4.3 and 25.2±4.5 Hz respectively. These values were calculated from the total number of action potentials generated over a minute. These values were not significantly different indicating the functional stability of the units studied. The conduction velocity was measured in 12 units at the completion of the protocol and found to be 34.1±4.3 m/sec.

Initially the effect of changes in oscillatory tidal volume on 25 stretch receptor units was studied with the oscillatory frequency pump setting at 17 Hz(Figure 6). The airway pressure and the oscillatory frequency were permitted to vary freely. As the oscillatory tidal volume was changed from 2.5 to 5.0 to 7.5 ml/kg the frequencies of

discharge from the stretch receptors increased from 22.8±4.7 to 36.2±5.6 to 44.6±6.8 Hz respectively; all these frequencies were significantly statistically different, both with parametric and non parametric testing. Although the oscillatory frequency was set at 17 Hz at these settings of oscillatory tidal volume the actual oscillatory frequencies were found to be 20.2±0.5, 16.9±0.1 and 14.1±0.4 Hz respectively; these changes were statistically different. In addition, the values for the mean airway pressures at these oscillatory tidal volume settings (and oscillatory frequencies) were found to be 1.3±0.2, 2.1±0.2 and 2.6±0.2 cm water respectively. The lowest value was significantly different from the other two (Figure 7).

Secondly, the effect of changes in oscillatory frequency on the same 25 units was studied. As the frequencies were varied from 8 to 18 to 28 Hz the oscillatory tidal volume was held constant at 5 ml/kg and the airway pressure was allowed to vary freely (Figure 8). At the above oscillatory frequencies the frequencies of discharge from the stretch receptors were 16.8±3.7, 33.0±4.5 and 36.6±5.4 Hz respectively; these values are all statistically different from each other, both by parametric and non parametric testing. Concurrent changes in mean airway pressure were 1.2±0.2, 2.1±0.2, 2.6±0.2 cm water the values again are all statisticaly different from each other (Figure 9).

Finally in 20 units the end expiratory pressure was varied with the oscillatory frequency set at 17 Hz and the oscillatory tidal volume set at 5 ml/kg. The control mean pressure was 2.1 cm water;

this was altered to 3.0, 6.0, 9.0 and finally 2.1 cm water in turn (Figure 10). The frequencies of discharge altered from 31.4±5.6 (initial control) to 46.8±8.5, 55.5±9.0, 53.7±9.4 and 23.0±3.5 (final control) Hz. The difference between the control values and the other values was significant, both by parametric and non parametric testing. There was no significant difference between the oscillatory frequencies (Fig. 11).

In this series it was apparent that variation in the principal parameter resulted in concurrent changes in the other parameters. In addition, it appeared that mean airway pressure seemed to have the greatest influence on the discharge from stretch receptors. Thus the data was re-analyzed to determine the possible influence of changes in airway pressure (either as a primary or a secondary change) on the activity of the stretch receptors. This analysis is presented graphically for high frequency oscillatory ventilation in Figure 12. From this data it became apparent that the changes in stretch receptor activity observed with variation in oscillatory frequency and oscillatory tidal volume could be, to a large extent, due to changes in airway pressure.

A two way analysis of covariance, compensating for the changes in airway pressure, however, indicated that the influences of oscillatory frequency and oscillatory tidal volume were significant (please see Discussion with respect to this analysis).

Protocol IA was the only section of the experiment conducted partially under α chloralose (5 dogs) and partially under phenobarbital (5 dogs) anesthesia. The results with both modes of

anesthesia were similar, although the mean values for the frequencies of discharge from the slowly adapting receptors tended to be higher, but not statistically so, during phenobarbital anesthesia. (The slowly adapting receptor frequencies of discharge during α chloralose and phentobarbital anesthesia during changes in oscillatory tidal volume were 17.6±3.4, 28.5±4.1, 33.1±3.1 Hz and 26.3±9.2, 41.4±8.8, 52.3±10.9 Hz respectively; during changes oscillatory frequency were 11.7±3.2, 29.4±4.6, 32.6±4.7 Hz and 20.3±5.8, 35.4±7.0, 42.7±8.4 Hz respectively;during changes in mean airway pressure were 20.4±4.1, 23.9±6.2, 29.3±5.6, 40.0±6.7, 19.2±3.5 Hz and 35.0±7.2, 54.4±10.5, 63.5±11.2, 58.3±12.2, 20.8±4.6 Hz). The data was pooled together for analysis.

Protocol IB. Slowly adapting stretch receptor discharge with individual alterations in oscillatory tidal volume, oscillatory frequency and mean airway pressure.

In the four experimental animals studied the heart rate and mean arterial pressure at the commencement of the protocol during intermittent positive pressure ventilation were 163.3±6.3 beats/min and 131.0±4.0 mm Hg. The arterial pH, PCO_2 PO_2 were 7.40±0.03, 28.7±2.4 mm Hg and 279.1±21.7 mm Hg respectively. The frequencies of discharge from slowly adapting stretch receptors during control intermittent positive pressure ventilation recordings, during the initial control period, after oscillatory tidal volume variation, and after oscillatory frequency variation were 27.9±3.7, 29.8±5.3, 28.1±4.4 Hz respectively. These frequencies were not significantly

different indicating the functional stability of the units.

The order of changes in the primary parameters was the same as in the first protocol. Sixteen stretch receptor units were studied. The oscillatory tidal volume was varied from 2.5 to 5.0 to 7.5 ml/kg with the mean airway pressure fixed at 3 cm water and the oscillatory frequency fixed at 16 Hz. The frequencies of discharge from the stretch receptors were 44.8±6.2, 48.2±6.3 and 49.0±6.0 Hz respectively. These frequencies were not significantly different, either by parametric or non parametric testing.

Next the oscillatory frequency was varied stepwise from 8 to 16 to 28 Hz with the mean airway pressure fixed at 3 cm water and the oscillatory tidal volume held constant at 5 ml/kg. The frequencies of discharge from the stretch receptors were 44.1±6.3, 46.6±5.8, and 52.5±6.7 Hz respectively. The latter value was different significantly from the other two, either by parametric or non parametric testing.

Finally, the mean airway pressure was varied from 3 to 6 to 9 and then again to 3 cm water. The oscillatory frequency was maintained at 16 Hz and the oscillatory tidal volume nominally held constant. The frequencies of discharge from the stretch receptors were 50.3±6.4, 69.8±8.3, 81.7±9.7, 52.8±6.4 Hz. The two values at 3 cm water were not statistically different , either by parametric or non parametric testing, but the values at the other setting were different. From these results it was concluded that the discharge from the stretch receptors was influenced mainly by the airway pressure and oscillatory frequency (Fig. 13).

Protocol I C. Combined effects of oscillatory frequency and mean airway pressure on slowly adapting stretch receptor discharge.

In the four experimental animals studied, the heart rate and mean arterial pressure at the commencement of the protocol during intermittent positive pressure ventilation were 163.3±10.0 beats/min and 147.0±5.6 mm Hg. The arterial pH, PCO_2 and PO_2 were 7.34±0.03, 39.7±5.4 mm Hg, 281.4±54.7 mm Hg respectively. A total of eight stretch receptor units were studied. The frequencies of discharge from the stretch receptors from the control periods during intermittent positive pressure ventilation were 26.5±1.4, 26.1±1.3, 25.8±1.4, 25.8±1.5 Hz respectively. These frequencies were not statistically different.

The bias flow was fixed in each run and the oscillatory tidal volume fixed at 5 ml/kg. At an oscillatory frequency of 8 Hz and mean airway pressures of 3, 5 and 7 cm water the frequencies of discharge from the slowly adapting stretch receptors were 36.7±2.7, 50.4±2.3 and 61.4±2.5 Hz respectively; at an oscillatory frequency of 16 Hz and mean airway pressures of 3, 5, and 7 cm water the frequencies of discharge from the stretch receptors were 42.2±2.4, 53.9±2.0 and 64.7±1.7 Hz respectively. At an oscillatory frequency of 24 Hz and mean airway pressures of 3, 5 and 7 cm water, the frequencies of discharge from the stretch receptors were 52.8±1.7, 58.4±2.1, and 67.5±1.7 Hz respectively. The split plot analysis of variance with frequency as the main variable showed the influences of oscillatory frequency ($p<0.05$) and of mean airway pressure ($p<0.01$) to be significant. There was also a significant interaction between the

effect of mean airway pressure and oscillatory frequency with each being greatest at the lowest level of the other parameter and diminishing as the other parameter increased (i.e. at the highest value of mean airway pressure the effect of changes in frequency was least) (Fig. 14).

Protocol II. Stimulation of Left Atrial Receptors During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

Protocol II A. Left atrial receptor heart rate reflex during intermittent positive pressure ventilation and high frequency oscillatory ventilation.

In five dogs at the commencement of the recordings the mean heart rate, systemic blood pressure, left atrial pressure and airway pressure were 95.4±11.9 beats/min, 121.0±8.2 mm Hg, 6.6±2.0 cm water and 4.2±0.4 cm water respectively. The arterial pH, PCO_2 and PO_2 were 7.39±0.2, 31.1±2.9 mm Hg and 231.7±35.5 mm Hg respectively.

In five dogs ten sequences of stretching the left atrial pulmonary vein junction were completed (Figures 15,16). The mean heart rate increase during twenty stimulations during intermittent positive pressure ventilation was 23.9±3.4 beats/min. On ten stimulations during high frequency oscillatory ventilation the heart rate increase was 24.5±5.4 beats/min (Figure 17). The responses were not statistically different, nor was a different result obtained if the intermittent positive pressure ventilation stimulations for each

run are averaged and then compared to those during high frequency oscillatory ventilation on that run (24.6±4.3 and 24.5±5.4 beats/min respectively). The increase after sectioning the ansa subclaviae with ten runs during intermittent positive pressure ventilation was 2.1±1.0 beats/min while during high frequency oscillatory ventilation in five runs the heart rate increase was 2.0±2.0 beats/min. These increases were not statistically significant, nor were they different from each other; however, they were different from the heart rate change prior to ansal sectioning.

There was no significant change in blood pressure or airway pressure with any of the stimulations; (Table 1) however, during both modes of ventilation there was a rise in left atrial pressure during stimulation. When the rise in left atrial pressure was compared to the heart rate increase and a linear regression obtained by the least squares method the correlation coefficient for either mode of ventilation was not significant (r=-.13 and r=.16 respectively). (Fig. 19). A rise in left atrial pressure post ansal sectioning, without an additional increase during stimulation was noted, this would not be expected to affect the reflex response. With the high frequency oscillatory system used, although no end expiratory pressure was intentionally applied, there was always a positive airway pressure.

The initial control heart rate during intermittent positive pressure ventilation was 89.9±6.7 beats/min, while during high frequency ventilation it was 112.7±11.3 beats/min, a difference that achieves statistical significance.

Protocol IIB. Left atrial receptor heart rate reflex with variable slowly adapting receptor discharge frequences (during high frequency oscillatory ventilation)

In five dogs when the recording commenced, the mean heart rate, systemic blood pressure, left atrial pressure and airway pressures were 68.2±6.6 beats/min, 110.8±9.7 mm Hg, 10.0±1.0 cm water and 4.6±5 cm water respectively. The inferior vena caval pressure was measured in 3 dogs at 9.0±1.0 cm water. The arterial pH, PCO_2, PO_2 were 7.37±0.02, 35.6±2.7 mm Hg and 178.3±42.7 mm Hg respectively.

In these animals the stimulation sequence described previously was repeated eight times. Thus a total of 24 stimulations during intermittent positive ventilation and eight sequences of varied parameters during high frequency oscillatory ventilation were completed. The heart rate increases (Table 2) with oscillatory tidal volume held constant and oscillatory frequency varied to 8, 16 and 25 Hz in turn were 16.0±1.7, 20.0±3.3 and 18.6±2.9 beats/minute respectively. The heart rate increases with oscillatory frequency held constant and oscillatory tidal volume varied to 2.5, 5.0 and 7.5 ml/kg in turn were 14.0±3.8, 17.6±3.3 and 19.3±2.5 beats/min. (Figure 20). Taken individually all these increases are significant, however, there is no statistically significant difference between the responses. The heart rate increases during intermittent positive pressure ventilation during inital control, mid protocol and final control were 20.0±3.5, 15.5±1.8, and 15.3±4.1 beats/min. There is no significant difference between the responses.

There was no significant difference in arterial blood pressure, left atrial pressure and inferior vena caval pressure measured at different volumes, frequencies and with or without stimulation. Although at any given setting the mean airway pressure did not vary with stimulation, there was a statistically significant increase in mean airway presure with increases either in oscillatory tidal volume or oscillatory frequency. The oscillatory volume in this protocol was 5 ml/kg, hence the mean airway pressure tended to be lower than in the first section where the oscillatory tidal volume was 7.5 ml/kg (Table 3). As in protocol IIA, the control heart rates were significantly higher during high frequency oscillatory ventilation, there was no significant difference between the heart rates at the various high frequency oscillator settings.

Arterial blood gases were taken at the various high frequency respirator settings. However, in the initial five sequences they were not taken at every setting. There was no statistical significance between the settings, however, a trend to a lower pH and higher PCO_2 was evident at lower settings of oscillatory tidal volume (Table 4).

Protocol II C. Left atrial receptor heart rate reflex with graded left atrial receptor stimulation during intermittent positive pressure ventilation and high frequency ocillatory ventilation.

In five dogs when the recording commenced, the mean heart rate, systemic blood pressure, airway pressure and left atrial pressure were 71.6±8.5 beats/min, 132.0±5.1 mm Hg and 2.8±0.4 cm water, and 9.9±1.5

cm water respectively. The arterial pH, PCO_2 and PO_2 were 7.39±.01, 32.7±3.4, mm Hg and 202.5±14.5 mm Hg respectively.

In ten runs of the stimulation sequence, during intermittent positive pressure ventilation, for three, two, and then one balloon, the heart rate increases were 29.8±6.0, 22.4±5.9 and 10.0±2.5 beats/min; the corresponding values during high frequency oscillatory ventilation (5 runs) were 25.9±7.1, 18.1±4.9, and 9.6±4.1 beats/min (Figure 21). If for the runs during intermittent positive pressure ventilation the initial and final control are averaged the values are 29.8±8.0, 22.4±8.3, and 10.0±3.3 beats/min; the mean values and significance were similar to those of the previous method of calculation. During both modes of ventilation there was a graded difference between the various levels of stimulation, however, a statistically significant increase was present only between one balloon and any other combination. There was no difference between the reflex response with either mode of ventilation.

Control heart rates for three, two and one balloon stimulations during intermittent positive presure and high frequency oscillatory ventilation were 90.7±5.2, 91.9±5.4, 88.7±4.9 and 109.6±9.2, 112.4±8.5, 118.4±10.7 beats/min. Although a marked trend was present, there was no statistical increase in control heart rate during high frequency ventilation. Evaluation of the other parameters, blood pressure, and mean airway pressure showed no significant differences with any control values compared to stimulation, different levels of left atrial stimulation and finally, no significant differences between modes of ventilation. Left atrial pressure and mean airway

pressure tended to be higher during intermittent positive pressure ventilation but these did not achieve statistical significance (Table 5).

Protocol II D. Left atrial receptor renal reflex during intermittent positive pressure and high frequency oscillatory ventilation .

Alternate animals were studied first during intermittent positive pressure or high frequency oscillatory ventilation.

In six dogs when the recordings commenced the mean heart rate, systemic blood pressure, left atrial pressure and mean airway pressure for three animals started on intermittent positive pressure and three animals started on high frequency ventilation were 105.3±11.5 beats/min, 109.3±5.9 mm Hg, 8.7±1.0 cm water 3.3±0.3 cm water and 120.7±8.6 beats/min, 112.5±106 mm Hg, 8.5±0.9 cm water 2.7±0.7 cm water respectively. The arterial pH, PCO_2, and PO_2 were 7.39±0.01, 38.8±2.5 mm Hg and 180.0±11.9 mm Hg respectively.

In these animals the stimulation sequence described previously was repeated a total of nine times during each mode of ventilation (Figures 22,23). The urine flow increased by a mean value of 7.3±2.0 ml/10 min segment during intermittent positive pressure ventilation and by a mean value of 6.5±1.4 ml/10 min segment during high frequency oscillatory ventilation. Taken individually, both of these changes are significant but no significant difference exists between them (Figure 24).

The total urinary sodium excretion increased by .88±.17 mEq/10 min segment during intermittent positive pressure ventilation and by .97±.24 mEq/ 10 min segment during high frequency oscillatory ventilation. Urine osmolality decreased by 251±55 mOsm/kg during intermittent positive pressure ventilation and by 259±46 mOsm/kg during high frequency oscillatory ventilation. Statistical significance for total urinary sodium and osmolality were as for urine flow. The urine sodium concentration decreased by 19.0±23.2 mEq/L during intermittent positive pressure ventilation and by 33.1±18.5 mEq/L during high frequency oscillatory ventilation, these changes were not significant (Table 6). The mean airway pressures during intermittent positive pressure and high frequency oscillatory ventilation were 3.1±0.2 and 2.7±0.4 cm water respectively (not significantly different).

Protocol III. Isolated Carotid Sinus Reflex Heart Rate Response During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

In five dogs when the recording commenced the mean heart rate, systemic blood pressure, and airway pressure were 109.3±23.2 beats/min, 118.8±2.5 mm Hg and 3.7±0.3 cm water respectively. The arterial pH, pCO_2 and pO_2 were 7.37±0.02, 33.9±2.0 mm Hg and 270.4±22.1 mm Hg respectively.

In these animals the sequence of altering the isolated carotid sinus pressure was repeated once in each animal; the heart rate

responses as a function of the pressure changes in the vascularly isolated carotid sinus were individually calculated for both modes of ventilation (Figure 25). The average percent heart rate changes per mm Hg change in carotid sinus pressure (range 84-224 mm Hg) during intermittent positive pressure ventilation was -1.06±0.09 and during high frequency oscillatory ventilation was -1.10±0.09. No significant difference was present (Figure 26). During high frequency ventilation the curve describing the relationship between carotid sinus pressure and heart rate was significantly shifted to the right.

Evaluation of systemic blood pressure and mean airway pressure showed no significant difference between the various carotid sinus pressure settings nor the two modes of ventilation (Table 7).

DISCUSSION

The results of the current study can be summed up under three headings, each corresponding to one of the protocols of the study: (1) determinants of stretch receptor discharge frequency during high frequency oscillatory ventilation (2) heart rate and renal response to stimulation of left atrial receptors during high frequency oscillatory ventilation and (3) heart rate response due to vascularly isolated carotid sinus pressure changes during high frequency oscillatory ventilation. In each of protocols two and three, high frequency oscillatory ventilation was the technique used to alter the discharge from the slowly adapting pulmonary stretch receptors in a quantitative and in a qualitative fashion (during variation in the ventilatory parameters of high frequency oscillatory ventilation as shown in protocol one). The effects of these changes in discharge were evaluated with respect to two well defined cardiovascular reflexes: (defined by the location of the afferent organs) the left atrial receptor reflex and the carotid sinus reflex. These were representative of the intracardiac (low pressure) and extra cardiac (vessel, high pressure) reflexes.

Protocol I. Determinants of Slowly Adapting Stretch Receptor Discharge Frequency During High Frequency Oscillatory Ventilation.

This protocol was divided into three subsections. It had been previously reported that during high frequency ventilation the discharge from the slowly adapting stretch receptors, which is

cyclical during intermittent positive pressure ventilation becomes continuous[169-170]. Further, it had been shown that during high frequency oscillatory ventilation the ventilatory efficacy is determined by oscillatory frequency, oscillatory tidal volume, bias flow and airway pressure[170]. In the current study where bias flow was fixed due to the nature of the respiratory circuit, variation in the other three parameters influenced the frequencies of discharge from the slowly adapting stretch receptors. In protocol IA oscillatory tidal volume, oscillatory frequency and mean airway were each altered in turn and the other variables were allowed to vary freely. Increases in any of the ventilatory parameters caused an increase in the frequency of discharge from the slowly adapting stretch receptors, however, due to the specific characteristics of the high frequency ventilatory circuit employed, primary changes in a given parameter resulted in secondary changes in the other parameters, i.e. primary increases in both oscillatory tidal volume and oscillatory frequency both increased mean airway pressure, and increases in oscillatory tidal volume decreased the oscillatory frequency. It is possible that these inter-relations were idiosyncrasies of the high frequency respiratory circuit used, however, they do indicate that changes in a single ventilator parameter will significantly alter the discharge frequency from the slowly adapting stretch receptors in a predictable fashion. Since, the same ventilatory circuit was used throughout the study, this would hold true for all protocols.

In this, as in all subsequent protocols, no attempt was made to

quantify changes in volume or the flow within the airways during high frequency oscillatory ventilation. Thus, at the level of the receptor the amount of local stretch of the tissue, which would be directly related to the transpulmonary pressure and hence the lung volume, was not known. The difficulties associated with quantification of this volume or flow have been mentioned in the Introduction with respect to intra lung volume shifts and the frequency response required for measuring instruments operative at these frequencies. With the high frequency ventilator used in this study, strobe light examination of the ventilator diaphragm showed a significant deformation during high frequencies. The the values given for oscillatory tidal volume were those that were determined by the manufacturer, (Metrex Inc.) for the volumes delivered at zero load (i.e zero mean airway presure) by a very slow manual movement of the eccentric cam mechanism. There can be no assurance that this volume remained the same at higher oscillatory frequencies, or airway pressure settings. This primary parameter setting was referred to as the oscillatory tidal volume. In addition to the above observations, it has been reported by other investigators with open circuits similar to the one employed in this study in that during high frequency ventilation the volume oscillated by the pump is not the volume oscillalted at the level of the airways since a variable proportion of this gas volume is lost down the bias flow tubing[167]. This is dependent on endotracheal tube size, airway resistance and numerous other factors. This problem may be partially remedied by regulating gas flow in the exhaust tube by the application of an exhaust vacuum and exhaust gas flow gauge[149]. However, even

if the volume of the gas oscillated at the external end of the endotracheal tube is known, the volume changes at the level of the slowly adapting stretch receptors, which may be affected by intrapulmonary gas flows, are unknown. Therefore any meaningful evaluation of the volume stimulus to the pulmonary stretch receptors must await further development in technology. (Ventilatory volume determinations for the other two modes of high frequency ventilation are equally difficult in that both use a narrow gas stream without a sealed endotracheal tube, thus gas additional to that in the stream may be brought into the lungs by the Venturi principle). In addition to the problems with frequency response mentioned above, the transducer available (Gould-Statham P23db) was intended for the measurement of blood pressure in a fluid filled system, hence with respect to airway pressure only the mean value was reported and the oscillations in pressure during high frequency ventilation were not commented on; a decrease in the frequency response of this system as compared to a fluid filled system would be expected.

The re-analysis of the data from protocol IA by an analysis of co-variance to statistically compensate for the multiple concurrent secondary changes with changes in the primary parameter (especially mean airway pressure changes with any other parameter change) did not show a conclusion different from the initial analysis. The analysis of co-variance was used in this instance as the best available test; strictly taken it could not be applied here since all the secondary changes occurred due to the same factor as that which caused the primary changes, hence they were not independent.

The non parametric tests, applied since the spread of the frequencies of stretch receptor discharges was so large; gave the same result as the parametric tests supporting that result.

In protocol IB the settings on the oscillatory ventilator were adjusted so that only the parameter of interest was allowed to change (except for oscillatory tidal volume, for which the pump setting was kept unchanged). Only oscillatory frequency and mean airway pressure had independent effects on the frequencies of discharge from the slowly adapting stretch receptors. This would suggest that the effect of changes in the oscillatory tidal volume on the frequencies of discharge from the slowly adapting pulmonary stretch receptors, in protocol IA, was via the concurrent changes in mean airway pressure and oscillatory frequency (probably the former since with the later the effect expected would be the opposite to that seen).

In protocol IC these two significant variables from protocol IB were investigated to determine the nature of any interaction between them. The oscillatory tidal volume pump setting was fixed. Not only did each of these variables have an independent effect on the frequencies of discharge from the slowly adapting receptors, but also the effect of each variable was greatest at the lowest value of the other. Overall, it was determined that in the experimental preparation used single increases of any of: oscillatory tidal volume, oscillatory frequency or airway pressure would increase the frequency of discharge from the slowly adapting pulmonary receptors but only the changes in airway pressure and oscillatory frequency were independent of changes in other parameters.

In protocol I, with the exception of five animals in protocol IA, the animals were anesthetized with pentobarbital sodium. In protocols II and III, and for the five animals in protocol I, chloralose was used. It is usual in experiments involving measurements of action potential frequency to use pentobarbital sodium, induction and maintenance are simplified and no metabolic acidocis or persistant acid-base abnormality due to the anesthesic agent occurs as with chloralose[30]. The cardiovascular parameters of heart rate and blood presure are both elevated during pentobarbital anesthesia (making it unsuitable for the study of cardiovascular reflexes which may be altered at grossly abnormal resting cardiovascular parameters) and some evidence exists for lack of response to left atrial receptor stimulation during pentobarbital anesthesia[174]. In protocol IA the frequency of action potential discharge from the slowly adapting stretch receptors tended to be higher during pentobarbital sodium administration, however, the responses with both anesthetics were stastically similar and are thus grouped together in this analysis since it is the trend of changes, rather than the actual numeric value (which varies greatly due to receptor location and subtype) that is important.

The suppressive effect of airway CO_2 on the intrathoracic stretch receptors is well described, the same suppressive effect may not hold for extrathoracic receptors. In all protocols arterial blood gases were periodically checked to monitor arterial PCO_2, no attempt at monitoring airway PCO_2 was made. Since bias flow was fixed and the rate of removal of CO_2 via the bias flow may be taken as constant at a

given setting, it may be assumed that the arterial PCO_2 reflected the highest alveolar value in the presumed gradient from the alveoli to the site of removal (the bias flow). In the protocols where the ventilator parameters were altered, IA, IB, IC, and IIB this arterial blood gas analysis would be of special importance. In protocol IIB where repeated measurements were taken, no statistically significant differences were present between the level of PCO_2 at the various settings although at lower oscillatory tidal volumes a trend to a respiratory acidocis was present. A significant change in the discharge frequency of the pulmonary slowly adapting stretch receptors was absent during oscillatory tidal volume changes suggesting that either the PCO_2 changes were not significant at the level of the alveoli or that if changes occurred (the changes in arterial PCO_2 were such that changes of a similar magnitude in the alveoli may be expected to change the receptor discharge) they were opposite to the oscillatory volume changes and hence compensated for them, this seems less likely at small oscillatory tidal volumes where with PCO_2 retention, the changes would be expected to be additive. This would make the first alternative more attractive.

In this study, since the purpose of evaluating the discharge frequency for lung receptors during high frequency ventilation was to use this information in a study of heart-lung interactions during physiological spontaneous respiration, only the slowly adapting stretch receptors were studied. These were defined by their discharge characteristics during intermittent positive pressure ventilation. The effect, if any on the other pulmonary receptors, myelinated and

unmyelinated during this mode of ventilation is not known. Studies into the effects of high frequency ventilation on damaged lungs or on lung function have not shown any deleterious effects which could predispose to activation of the other receptors. Airway pressure was kept within the range of the slowly adapting receptors.

In speculating on the findings from protocol I it is likely that in the case of increases in receptor discharge with increases in mean airway presure the static component of receptor discharge increased. In the case of oscillatory frequency the dynamic component of receptor discharge may have been more important in determining the overall activity, however, an element of air trapping could have increased the static component. No attempt was made to differentiate between these two possible influences. The absence of flow and volume measurements makes speculation on the lack of effect due to changes in oscillatory tidal volume more difficult. It is possible that no changes in oscillatory tidal volume occurred at the level of the airways or that the dynamic and static components changed in such fashion that they compensated for their respective influences.

In summary, protocol I indicated that high frequency oscillatory ventilation altered the dischage from pulmonary stretch receptors, at the level of the cervical vagal nerve, in a predictable fashion. An interaction between the pump parameters was also discovered.

Protocol II. Stimulation of Left Atrial Receptors During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

Having confirmed in protocol I that qualitative changes occurred during high frequency ventilation in the discharge frequency from slowly adapting stretch receptors and having demonstrated that quantitative changes in this discharge could be brought about by altering the parametrs of gas exchange during high frequency ventilation, protocol II was undertaken to evaluate the effect of this altered discharge (qualitatively and quantitatively) on the left atrial receptor low pressure cardiovascular reflex. Four sets of experiments were done, the first three investigated the reflex tachycardia while the last investigated the renal response.

In the first set, protocol IIA, it was ascertained that the reflex tachycardia that is well described during intermittent positive pressure ventilation with left atrial receptor stimulation is present during high frequency oscillatory ventilation and that it is abolished by the same procedure; sectioning of the ansa subclaviae; the efferent limb of the reflex; as during intermittent positive pressure ventilation. During both modes of ventilation there was a significant rise in left atrial pressure during the stimulations. The mean increase with intermittent positive pressure ventilation was 1.0 while that with frequency ventilation was 1.9 cm of water. There was no associated fall in mean systemic blood pressure, nor did the rises in heart rate correlate with the heart rate response. It is unlikely that the increase in heart rate could be due, therefore, to a systemic

hypotension secondary to left ventricular inflow obstruction. The systemic blood pressure and airway presure were similar during both modes of ventilation, however, the resting heart rate during high frequency ventilation was significantly higher than during intermittent positive pressure ventilation. This change in resting heart rate in the absence of baroreceptor activation suggests a higher resting sympathetic stimulation (or alternatively and less likely, a lesser parasympathetic stimulation of the heart). The mechanism of such an altered baseline status is unclear but will be discussed later. Although the reflex tachycardia due to left atrial receptor stimulation may not be equivalent at all resting heart rates, since the goal of this protocol was simply to evaluate the peristance of this reflex during high frequency ventilation this resting difference is irrelevant.

Following ansal sectioning a significant elevation of left atrial pressure was present during high frequency ventilation. This may represent onset of relative left ventricular dysfunction secondary to loss of inotropic sympathetic stimulation of the left ventricle during a period when there are changes in sympathetic tone elsewhere (as manifested by altered resting heart rate). However, since there was no reflex heart rate response there is no special significance to this observation except to suggest a hemodynamically significant alteration in sympathetic tone during high frequency oscillatory ventilation.

In protocol IIB it was demonstrated that changing the slowly adapting stretch receptor activity either by increasing the oscillatory tidal volume or oscillatory frequency did not

significantly alter the reflex tachycardia due to left atrial receptor stimulation. The range of oscillatory tidal volumes and frequencies was selected on the basis of the previous work, and the mean oscillatory tidal volume setting was 5 ml/kg as compared to 7.5 ml/kg in protocol I. This resulted in lower mean airway pressures. Although the range of ventilator settings was determined on the basis of the maintenance of adequate gas exchange a mild acidocis occurrred at an oscillatory volume of 2.5 ml/kg and it is possible that the mildly reduced increase in heart rate at this setting could be a consequence (not a statistically significant reduction).

Left atrial pressures were higher in this series than in protocol IIA, it is possible that with the lower airway pressures there was less of an obstruction to venous return and hence better cardiac filling as compared to protocol 11A, alternatively it is possible the animals were better hydrated. There was no significant difference in the inferior vena caval pressure, in the three dogs in which this was studied, between the two modes of ventilation. As in protocol IIA there was a significant heart rate increase with the commencement of high frequency ventilation, however, once on this mode of ventilation the control heart rates and the responses to stimualtion were statistically equal. As expected from protocol IA airway presure increased during increases of either oscillatory tidal volume or oscillatory frequency.

In protocol IIC it was shown that, as had been previously demonstrated during intermittent positive pressure ventilation, increasing the amount of left atrial receptor stimulation by

increasing the number of left atrial sites stimulated would result in an increase in the reflex tachycardia. Again, the heart rates, during the control periods on intermittent positive pressure ventilation were lower than for similar periods during high frequency ventilation.

In the final section of the protocol, IID, it was demonstrated that the renal response to left atrial receptor stimulation consisting of a hyposmolar diuresis and naturiesis that is described during intermittent positive pressure ventilation was preserved during high frequency oscillatory ventilation. Again, a non statistically significant increase in the control heart rate during high frequency ventilation was present.

Protocol III. Isolated Carotid Sinus Reflex Heart Rate Response During Intermittent Positive Pressure and High Frequency Oscillatory Ventilation.

The third protocol investigated the effect of a qualitative change in the discharge from slowly adapting stretch receptors (that from cyclical to continuous) on the reflex heart rate response due to pressure changes within a vascularly isolated carotid sinus with the systemic pressure and hence the aortic baroreceptor stimulation fixed. It was found that the percent heart rate change per mm Hg carotid sinus pressure change was unaltered during high frequency ventilation compared to intermittent positive pressure ventilation. The curves defining this relationship, however, were not identical in that during high frequency ventilation the curve was shifted to the

right indicating a higher carotid sinus threshold. This relationship persisted throughout the range of carotid sinus pressures studied and may again be a manifestation of an increased sympathetic tone during high frequency ventilation either via a direct mechanism on the carotid sinus receptors or by a change in the properties of the carotid sinus wall musclature.

Conclusion

It can be concluded that: (1) during high frequency ventilation the discharge of the slowly adapting stretch receptors is not only altered qualitatively (becoming continuous rather then cyclical) but also may be altered quantitatively by altering the parameters of gas exchange during high frequency oscillatory ventilation (2) the altered stretch receptor discharge does not interfere with the functional integrity of the left atrial receptor reflex (in an open chest preparation) nor the carotid sinus baroreceptor reflex.

Through the course of the experiment control heart rates taken during high frequency ventilation were higher than those during intermitent positive pressure ventilation. There was no difference in control heart rates at different high frequency parameter settings (Table 2). Reports from other studies of high frequency ventilation have not commented on this[155,158,159]. In addition, in protocol IIA following efferent denervation by sectioning of the ansa subclaviae and removing the inotropic stimulus to ventricular function appeared to bring about relative left ventricular dysfunction during high frequency but not during conventional ventilation. In protocol III a

higher carotid sinus threshold and curve of operation was found suggesting that a decreased parasympathetic tone was not the likely mechanism. These findings taken together indicate a higher control sympathetic tone during high frequency ventilation; this may be due to obstruction to venous return since during this mode of ventilation airway pressure is positive and unchanging. However, in protocol IIB, where in three animals the inferior vena caval presure was measured, no evidence for such a hypothesis was found. It is possible that in a larger sample, evidence of caval obstruction could be found. Other mechanisms, perhaps even the altered pulmonary stretch receptor discharge (which at any mean airway presure is increased during high frequency ventilation)[170] increases the resting sympathetic tone. Previous work[124] has shown significant augmentation of sympathetic fiber discharge during central respiratory center discharge, i.e. during phrenic nerve discharges (in a cat model with cut vagi) and more recently it has been suggested that pulmonary afferent activity influences this central respiratory modulation of sympathetic discharge[125]. In this latter work, however lung inflation decreased sympathetic discharge. In the current work, respiratory center activity was not monitored, however, it is known that with high frequency oscillatory ventilation phrenic activity[170] and perhaps respiratory center activity is suppressed. The effect of pulmonary afferents may be greater in this setting. In spite of the fact that the two experiments (124,125) above do not seem to be in agreement on the timing of changes in sympathetic discharge, it may be speculated that if the cardiovascular sympathetic outflow increases (i.e.

inspiratory increase in heart rate with sinus tachycardia) with lung distension; then during high frequency ventilation this may cause a chronic increase in sympathetic tone. Since evaluation of this phenomenon was not the aim of the experiments, no definite conclusions, as its etiology, can be drawn from the results obtained.

The aim of this study was to determine the effect of altered slowly adapting stretch receptor discharge during high frequency ventilation on cardiovascular reflexes; the possibility of other receptor activation and subsequent interactions was not directly addressed. It is not known if high frequency ventilation alters the discharge from left atrial receptors (or other intracardiac receptors both atrial and ventricular) or from the carotid sinus (located in close proximity to the oscillating trachea), further it is not known if the normal function of these receptors requries the respiration associated cyclical variation in cardiovascular volumes and presures. However, since respiratory influences are not the normal stimuli for the cardiovascular receptors it is not likely that the change in ventilation directly affects the function of these receptors to a significant degree. Incidentally, during high frequency oscillatory ventilation, there is no sinus arrhythmia, however, this observation does not clarify the mechanism of this phenomenon due to the multiple changes with this mode of ventilation. In every protocol, it appeared that the resting level of sympathetic tone during high frequency ventilation was higher; this could predispose to changes in reflex cardiovascular arc function that would tend to minimize the direct effects of high frequency ventilation (it is known

that the carotid sinus has efferent sympathetic innervation).

On the respiratory side, as mentioned previously, care was taken in protocol I to study only slowly adapting stretch receptors. The role of chest wall receptors[80,175], or chest musclature receptors, or of the other lung receptors during high frequency ventilation is not known. Rapidly adapting (or irritant or cough) receptors[76] also conduct via myelinated nerves, however, their discharge during control periods are irregular, both with respect to the respiratory cycle and pattern. Their natural stimulus appears to be either mechanical or chemical irritation. As with slowly adapting receptors, their activity is inversley related to lung compliance[176] suggesting that transpulmonary pressure is an important factor in regulating their discharge. The non-myelinated fibers, divided into either J receptors or bronchial C fibers, lack any respiratory modulation in open chest artificially ventilated dogs even where the inflating pressure exceeds 10 cm water[177], a level not reached as the mean airway presure in this study. Sympathetic afferents may exist from the lung, little is known with respect to their normal function. It is possible, that one or more of these receptors was activated during this non physiological mode of respiration, and that the effect of its discharge compensated for any changes that would have occurred due to discharge from the slowly adapting stretch receptors. It is also possible that the postulated rise in sympathetic tone was due to the stimulation of some of these receptors i.e. chest wall musculature receptors may help raise sympathetic tone during exercise.

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With respect to the central pathways and connections of these

reflex arcs, no brain stem investigations were done to determine if any interaction occurred at a neuronal level or what the medullary nerve traffic pattern was. The altered pulmonary discharge during high frequency ventilation was documented at the level of the cervical vagus, it was assumed that at the site of integration of the cardiovascular and pulmonary reflexes, after initial neuronal processing, no marked alteration had occurred in comparison to the cervical vagal nerve traffic.

Both of the cardiovascular reflexes investigated in this study, the low pressure intracardiac left atrial receptors and the high pressure vessel carotid sinus baroreceptors, are important in the maintainance of cardiovascular homeostasis. When their function becomes disordered deficiencies in regulation can exist that may be seriously detremental to the animal. In human clinical work high frequency oscillatory ventilation has been used for ventilating critically ill patients in whom any further instability may not be tolerated. Adequate functioning of all reflex mechanisms is required in all such patients. The current investigation showed that the functional integrity of two specific reflexes was not disturbed by high frequency oscillatory ventilation. Moreover, it may be possible to extrapolate that since cardiovascular homeostasis was maintained in these animals, no net significant effect on cardiac reflex regulation was caused by this mode of ventilation. This finding is important in the clinical applications of high frequency oscillatory ventilation. Clinical studies with this mode of ventilation have also not reported significant cardiovascular pulmonary interactions, as would be

expected from the current study.

It would be incorrect to state that based on the work presented, no effect of the respiratory system exists on the cardiovascular system within the physiological range of each system. Current evidence strongly suggests altered sympathetic tone during high frequency oscillatory ventilation, this effect may not be due to mechanical obstruction to venous return but to central events; the abolition of sinus arrhythmia during high frequency oscillatory ventilation does not provide an explanation for the occurrence but suggests that high frequency ventilation interferes at some site in the genesis of this phenomenon.

Only two reflexes out of a great number of cardiovascular reflexes were evaluated. Not all reflexes are equally susceptible in the same fashion to other influences, i.e. in studies during intermittent positive pressure the blood presure response to changes in isolated carotid sinus pressure was modified but little change was noted in the heart rate response[178]. It is entirely possible that an effect of altered discharge from pulmonary stretch receptors exists for other reflex arcs, or different aspects of the reflex arcs studied in this work.

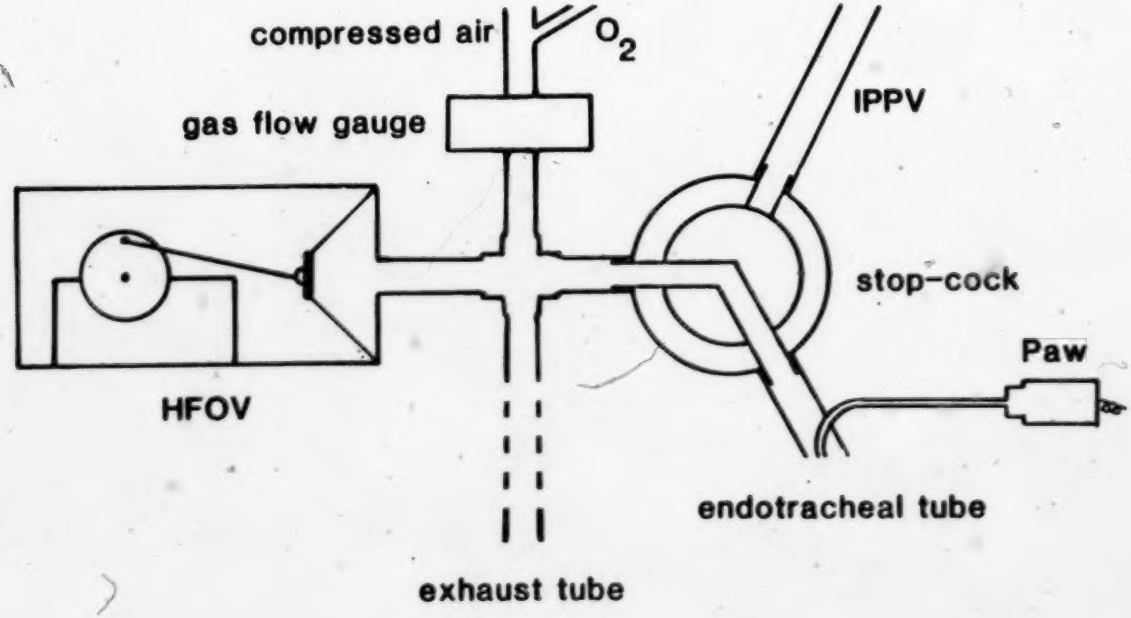

FIGURE 1 HIGH FREQUENCY OSCILLATORY VENTILATION CIRCUIT: High frequency oscillatory ventilator with an eccentric cam driven rubber diaphragm is shown on the left. It is connected to a bias flow arrangement and a a three way stop-cock to permit connection of the animal to either of intermittent positive pressure or high frequency oscillatory ventilation.

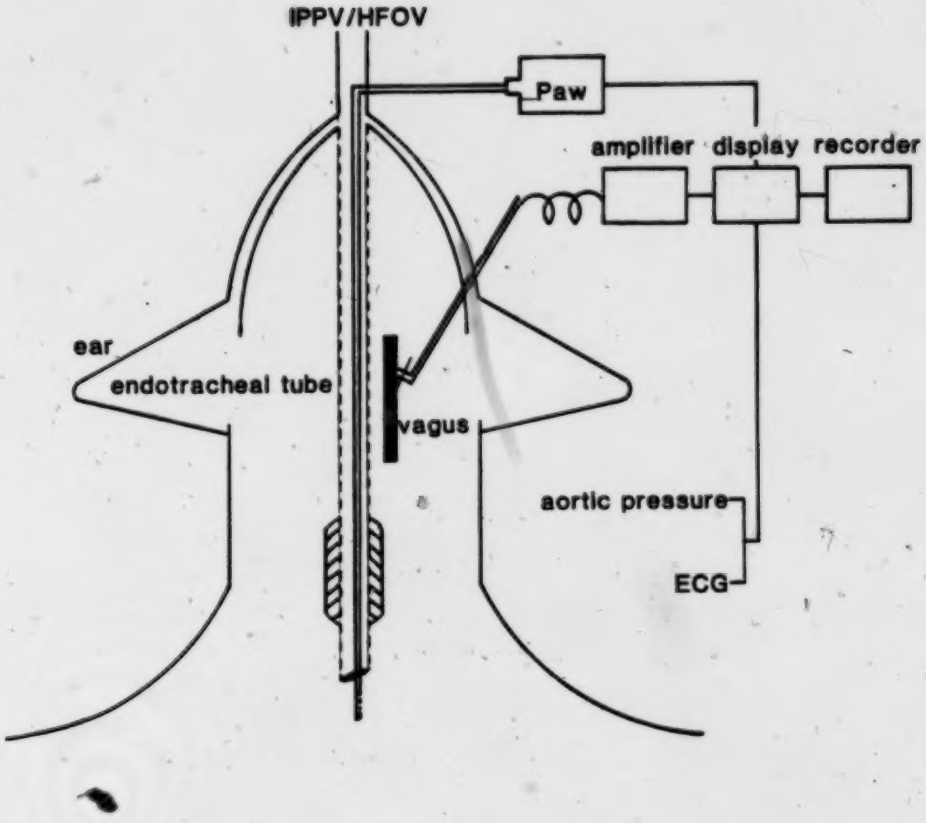

FIGURE 2 VAGAL NERVE RECORDING PREPARATION: A section of desheathed cervical vagus nerve is shown. Recordings were taken from afferent nerve fibers from slowly adapting stretch receptors (identified by the typical discharge pattern during intermittent positive pressure ventilation of single unit fibers.).

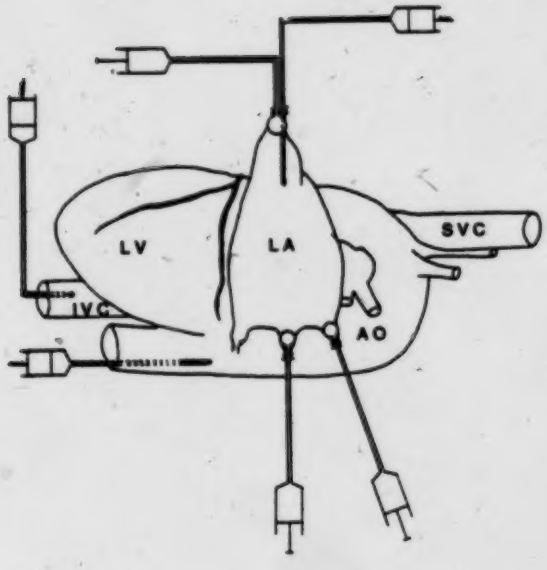

FIGURE 3 LEFT ATRIAL RECEPTOR STIMULATION (HEART RATE RESPONSE) PREPARATION: The heart is illustrated; (LV) left ventricle, (LA) left atrium, (SVC) superior vena cava, (AO) aorta, (IVC) inferior vena cava. Small latex balloons were placed at each of the left upper and left middle pulmonary vein-atrial junctions and a larger balloon was inserted into the left atrial appendage. Pressures were measured in the left atrium, aorta, and in protocol 11B in some animals in the inferior vena cava. Distension of the balloons stimulated the left atrial receptors.

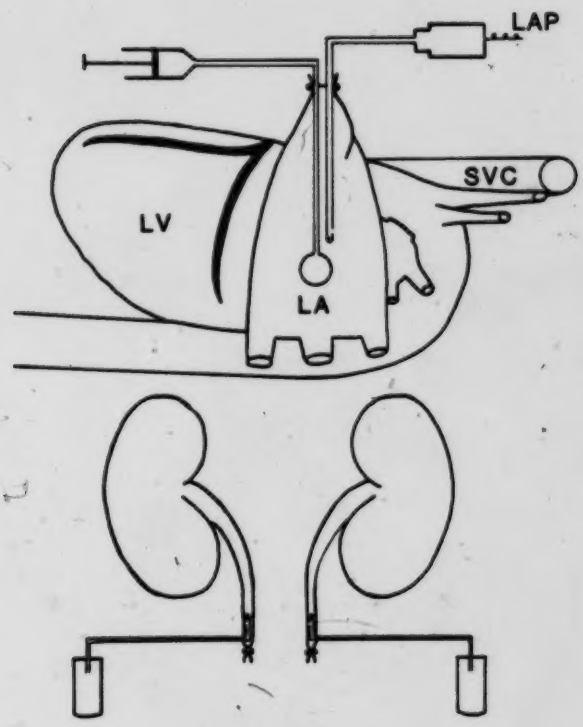

FIGURE 4 LEFT ATRIAL RECEPTOR STIMULATION (RENAL RESPONSE) PREPARATION: Abbreviations as in Figure 3; (LAP) left atrial pressure. A single large latex balloon was inserted into the left atrium to obstruct the mitral valve while inflated. The ureters were cannulated to collect urinary output over ten minute intervals. Inflation of the balloon caused a stimulation of left atrial receptors.

FIGURE 5 CAROTID SINUS STIMULATION PREPARATION: Abbreviations: (CSP) carotid sinus pressure, (I. C.) internal carotid, (E. C.) external carotid, (O. A.) occipital artery, (C. C.) common carotid, (BP) systemic blood pressure, (C1) container number one, (C2) container number 2, (C3) container number three, (P1) pump number one, (P2) pump number two. The carotid sinuses were vascularly isolated and cannulated with a "u" shaped cannula that permitted both pressure monitoring in the carotids and a non-pulsatile flow taken from the arterial reservoir (C1) via a roller pump (P1) and then via a pressure dampening chamber (C3) to be infused. The left femoral artery was connected to the arterial reservoir (C1), which had a water heater to maintain the blood temperature, and in which a constant air pressure was maintained by means of a balance between an inflow of pressurized air and a leak of this air via an adjustable valve. Fluid from a third chamber (C2) was returned to the arterial chamber (C1) by the same roller pump (P1) to replace fluid infused into the carotids. Systemic blood pressure was measured.

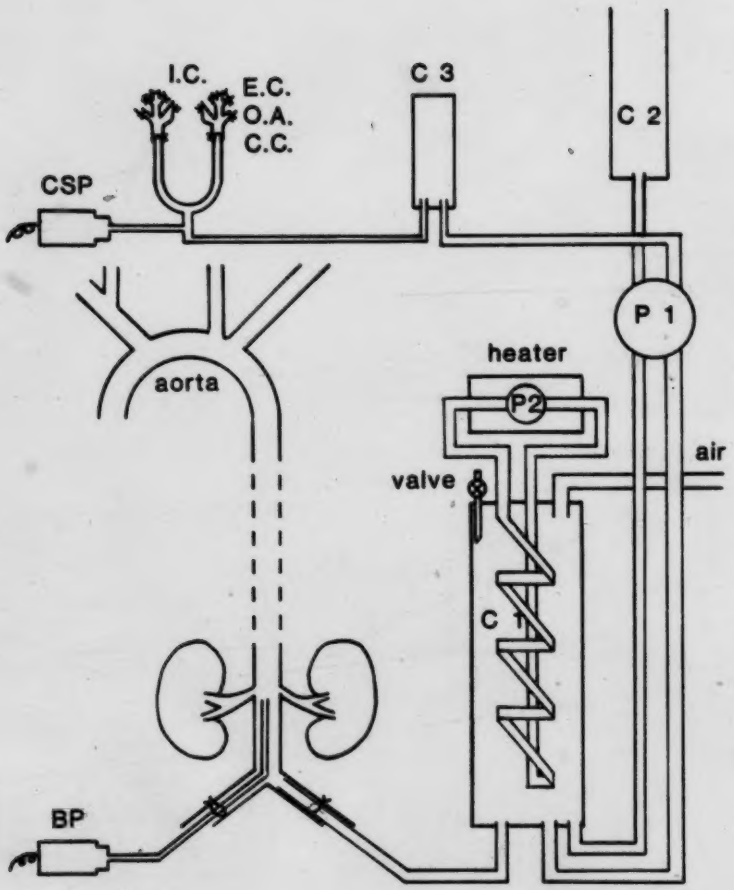

FIGURE 5 CAROTID SINUS STIMULATION PREPARATION

FIGURE 6 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE RECORDINGS DURING VARIATION IN OSCILLATORY TIDAL VOLUME: Abbreviations: (Act. Pot.) action potentials recorded in the cervical vagus from slowly adapting pulmonary stretch receptors, (Paw) mean airway pressure, (O. T. V.) oscillatory tidal volume, (O. F.) oscillatory frequency, (B. F.) bias flow, (V.) tidal volume, (F.) respiratory frequency. Five panels are shown, in each the upper half shows the single fiber afferent nerve action potentials recorded from myelinated cervical vagal nerve fibers and the lower tracing shows airway pressure. The first and fifth recordings are during intermittent positive pressure ventilation; the middle three are during high frequency oscillatory ventilation, the first with an oscillatory tidal volume of 2.5 ml/kg, the second wiht 5.0 ml/kg, the third with 7.5 ml/kg. The pump oscillatory frequency was set at 16 Hz but varied with the oscillatory tidal volume. Airway pressure was noted to increase with oscillatory tidal volume. Bias flow was fixed. The qualitative change in action potential discharge from intermittent to constant is evident as is the qualitative increase in action potential frequency with increasing oscillatory tidal volume. In the panels recorded during high frequency oscillatory ventilation the airway pressure is initially shown as phasic and then electronically meaned.

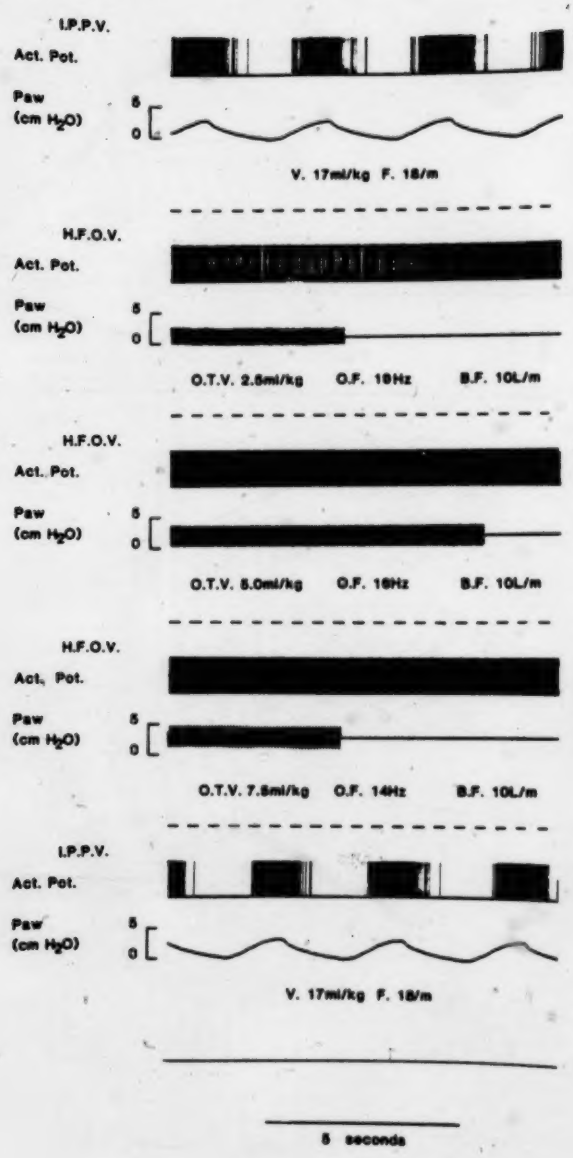

FIGURE 6 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE RECORDINGS DURING VARIATION IN OSCILLATORY TIDAL VOLUME

FIGURE 7 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING VARIATION IN OSCILLATORY TIDAL VOLUME: Abbreviations as in Figure 6. Abcissa: oscillatory tidal volume (ml/kg), Ordinate: frequency of discharges from the slowly adapting stretch receptors in action potentials recorded from the cervical vagus (Hz). Under the abcissa are concurrent changes in oscillatory frequency (Hz) and airway pressure (cm water) at each setting of the oscillatory tidal volume. Statistical significance ($p<0.05$) is indicated by the stars (★); in the data for oscillatory tidal volume and oscillatory frequency it is given with respect to the mid value, in the case of airway pressure it is as indicated. The stretch receptor discharge was different from the mid setting at both high and low oscillatory tidal volume settings, however, the oscillatory frequency was also different at these settings. The airway pressure was different between the lowest and any other setting of the oscillatory tidal volume.

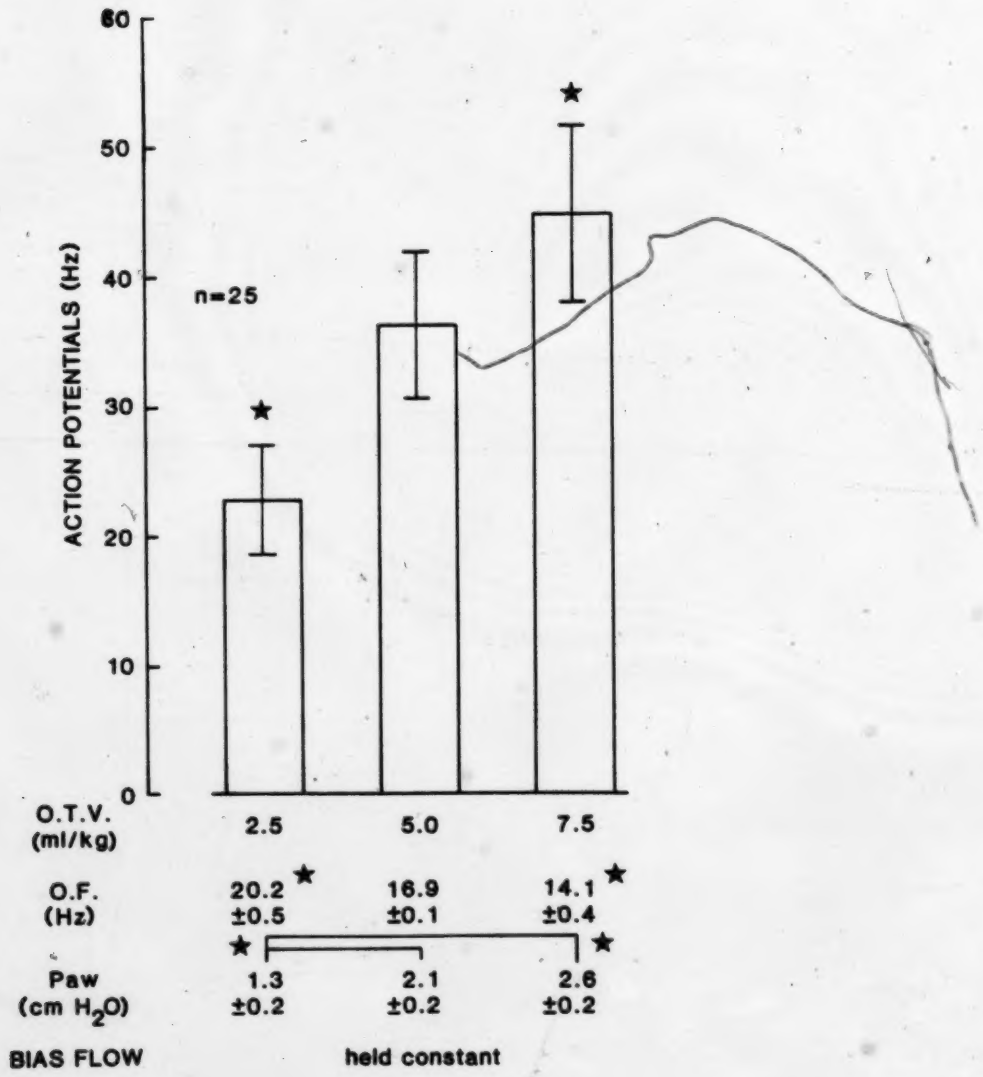

FIGURE 7 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING VARIATION IN OSCILLATORY TIDAL VOLUME

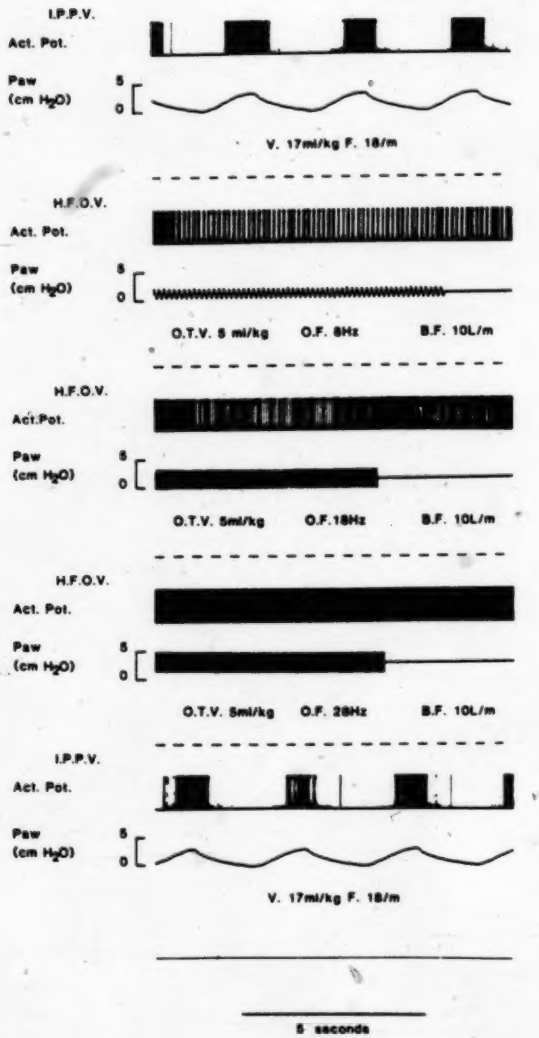

FIGURE 8 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE RECORDINGS DURING VARIATION IN OSCILLATORY FREQUENCY: Abbreviations and arrangement are as in Figure 6. A similar increase in action potential frequency with increased oscillatory frequency from 8 to 18 to 28 Hz was present. Airway pressure increased with increasing oscillatory frequency. Bias flow was fixed. Oscillatory tidal volume was at a fixed ventilator setting.

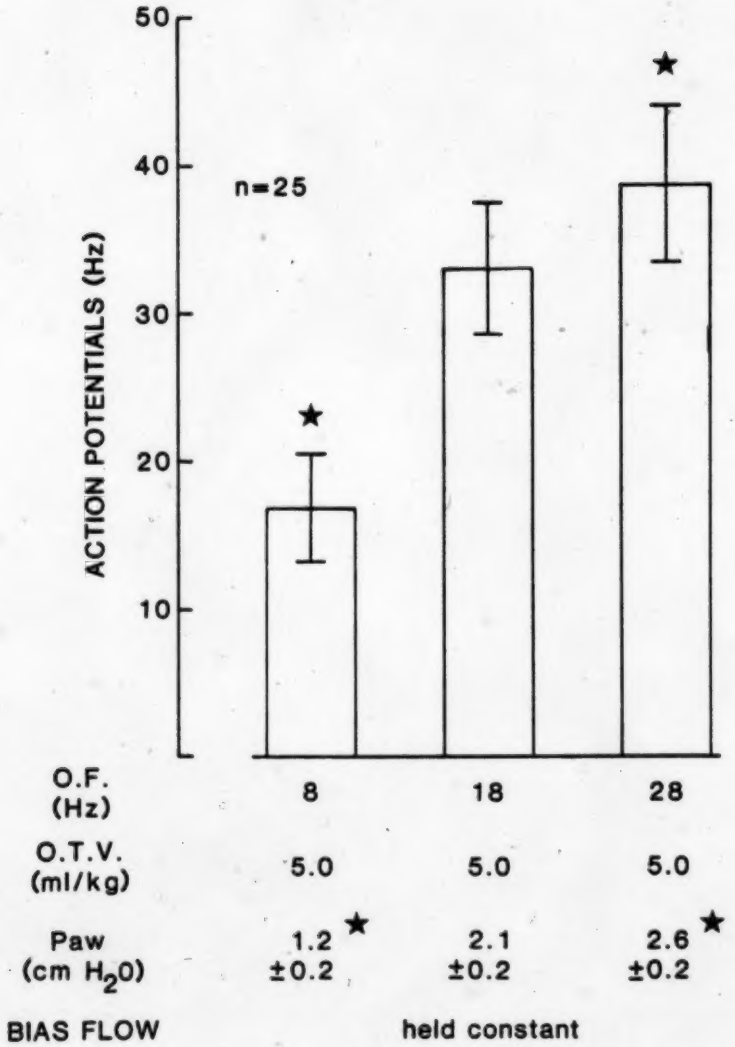

FIGURE 9 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING VARIATION IN OSCILLATORY TIDAL VOLUME: Arrangement similar to Figure 7. The stretch receptor discharge frequency was different at both high and low oscillatory frequency settings as compared with control, however, so was the airway pressure. The oscillatory tidal volume pump setting was fixed as was the bias flow.

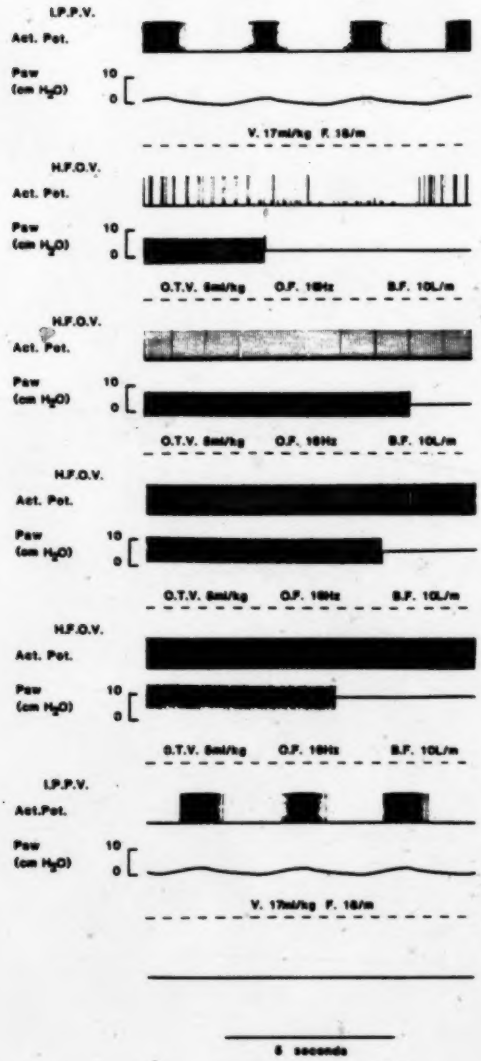

FIGURE 10 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE RECORDINGS DURING VARIATION IN MEAN AIRWAY PRESSURES: Abbreviations and arrangement are similar to Figure 6. A similar quantitative increase in action potential frequency with increased airway pressure from 3 to 6 to 9 cm water was noted. Oscillatory frequency was unchanged and bias flow and the pump setting of oscillatory tidal volume were fixed.

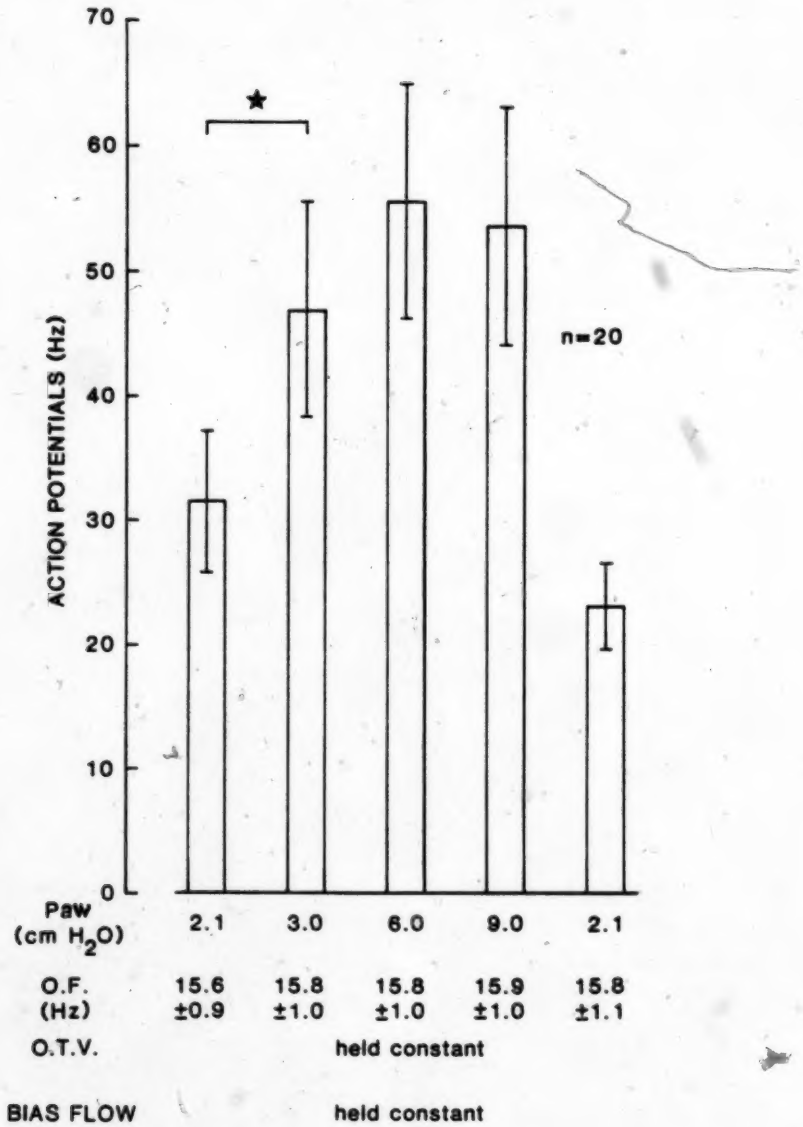

FIGURE 11 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING VARIATION IN MEAN AIRWAY PRESSURE: Arrangement is similar to Figure 7. The stretch receptor discharge frequency was different at all levels of airway pressure compared with control. There was no change in oscillatory frequency. The oscillatory tidal volume pump setting was fixed as was the bias flow.

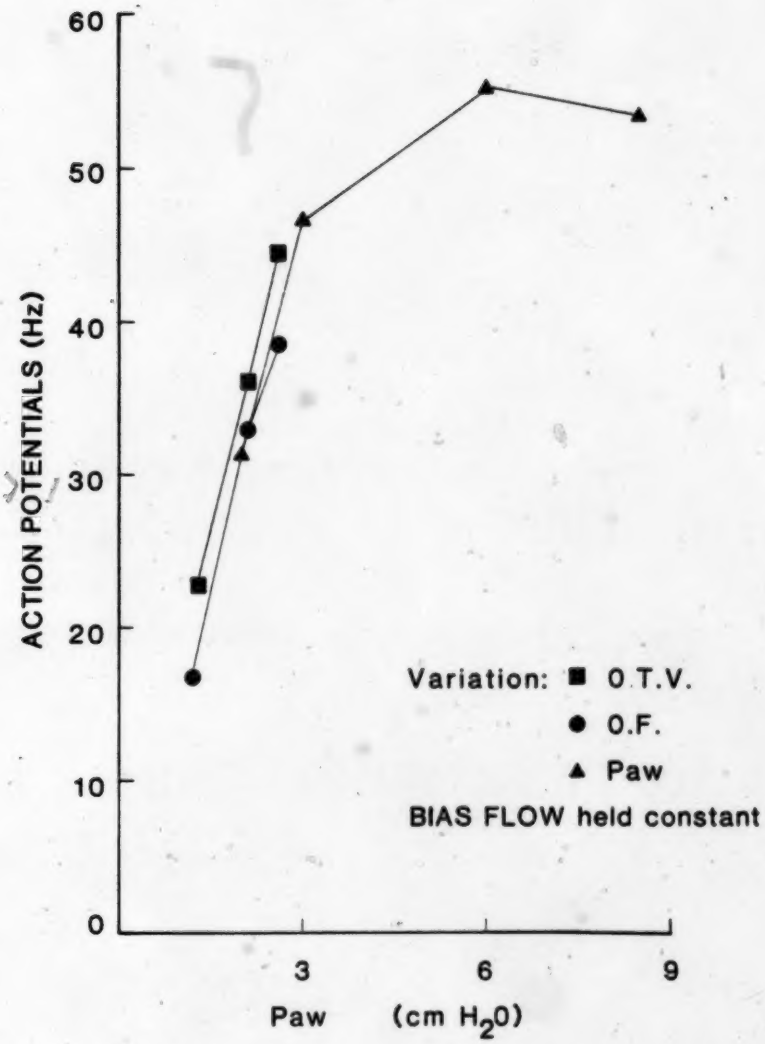

FIGURE 12 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES WITH CONCURRENT VARIATION IN MEAN AIRWAY PRESSURE: Abcissa: mean airway pressure (cm water), Ordinate: frequency of discharges from the stretch receptors recorded as action potentials in the cervical vagus (Hz). Abrreviations as in Figure 6. Changes in any primary parameter produced a concurrent increase in airway pressure and a similar increase in stretch receptor discharge.

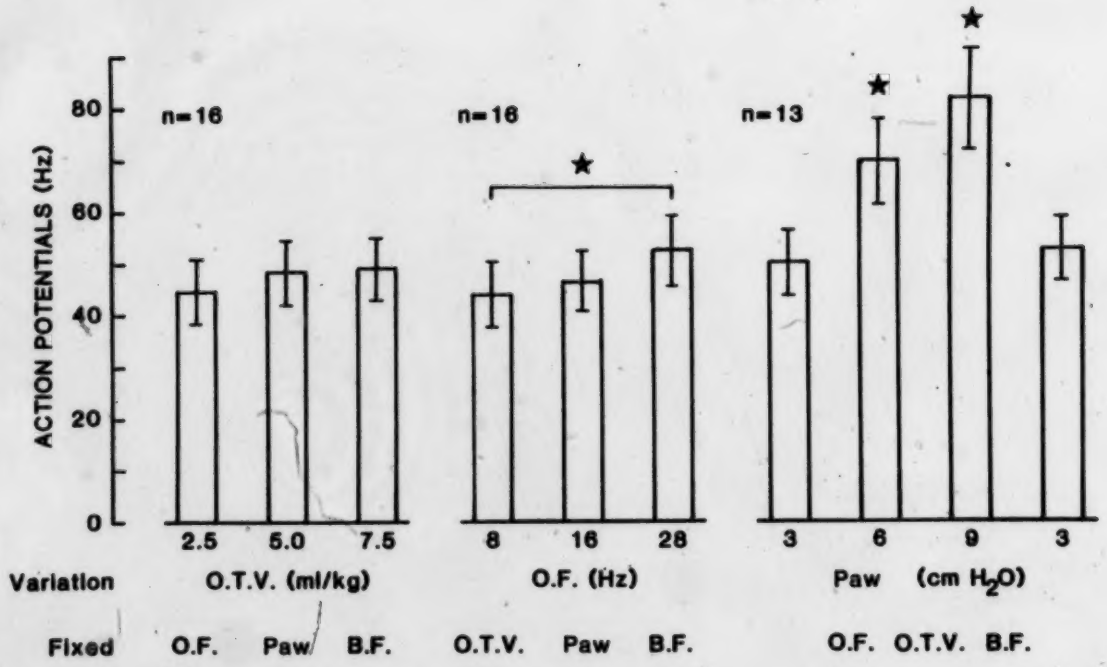

FIGURE 13 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING SINGLE PARAMETER VARIATION: Abbreviations as in Figure 6. Abcissa: sequential variation in oscillatory tidal volume (ml/kg), oscillatory frequency (Hz) and airway pressure (mm Hg). Ordinate: frequency of discharges from stretch receptors recorded from the cervical vagus (Hz). Only during increases in oscillatory frequency and airway pressure was the stretch receptor discharge increased. Statistically significant ($p<0.05$) changes are indicated by the stars (★).

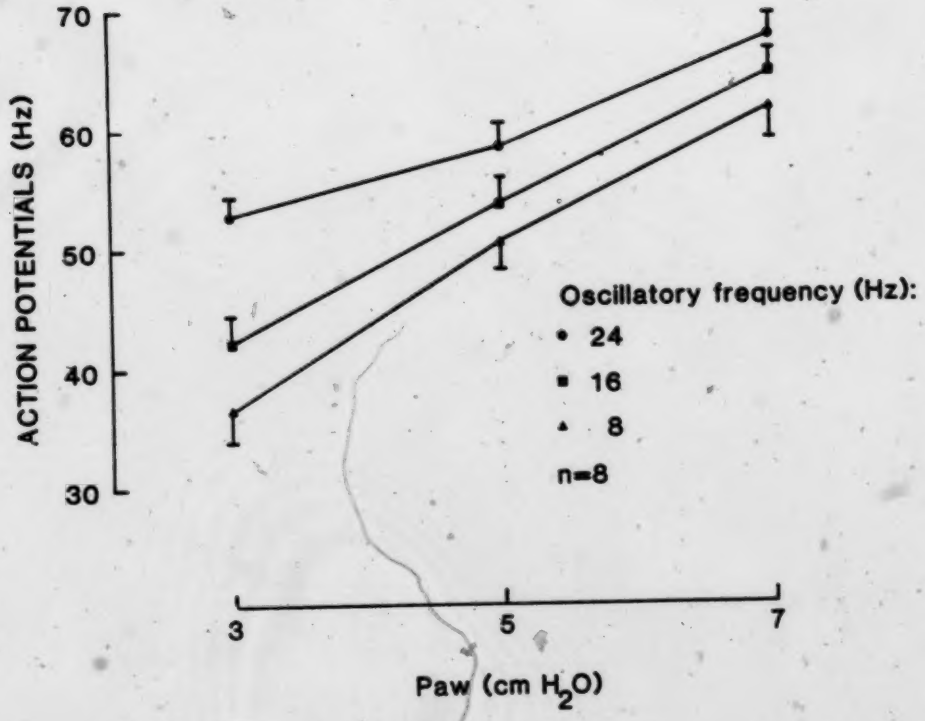

FIGURE 14 SLOWLY ADAPTING STRETCH RECEPTOR DISCHARGE FREQUENCIES DURING VARIATION IN MEAN AIRWAY PRESSURE AND OSCILLATORY FREQUENCY: Abcissa: mean airway pressure (cm water); Ordinate: frequency of discharge from stretch receptors recorded from the cervical vagus (Hz). Split plot analysis of the effect of airway pressure and oscillatory frequency on the frequency of discharges from slowly adapting stretch receptors. Differences were significant between all airway pressures and all oscillatory frequencies.

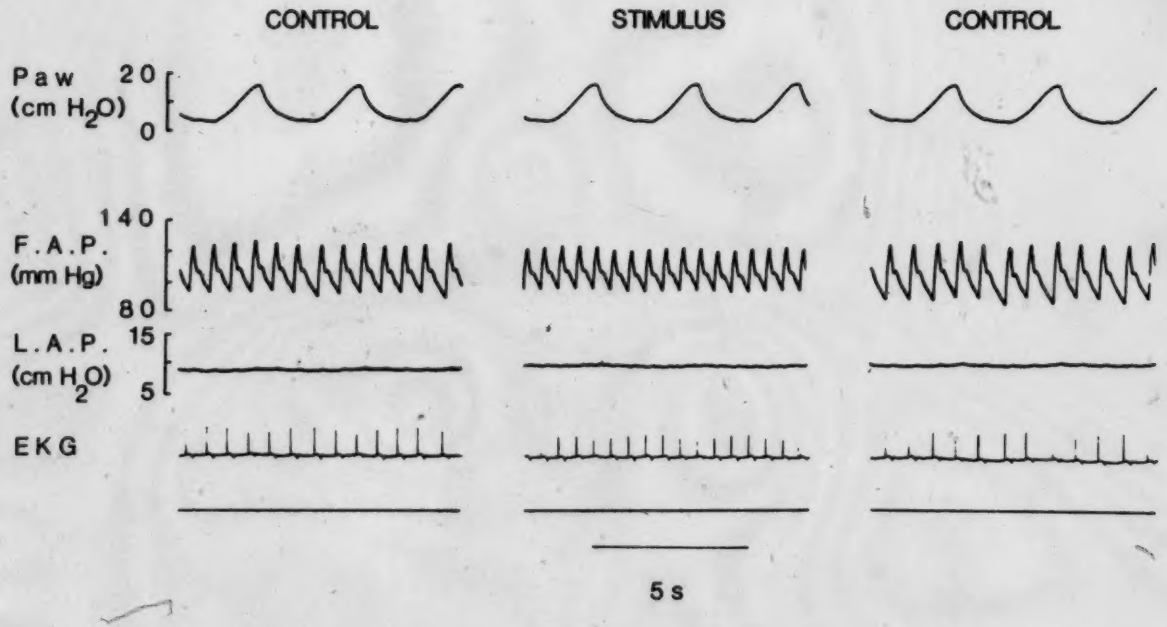

FIGURE 15 HEART RATE RESPONSE DURING INTERMITTENT POSITIVE PRESSURE VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations: (Paw) airway pressure, (F. A. P.) femoral artery pressure, (L. A. P.) left atrial pressure, (EKG) electrocardiogram, (S) seconds. Ten second typical panels of control, stimulation and final control are shown. The heart rates were 82, 99 and 72 beats/min respectively; no significant change occured in the other parameters.

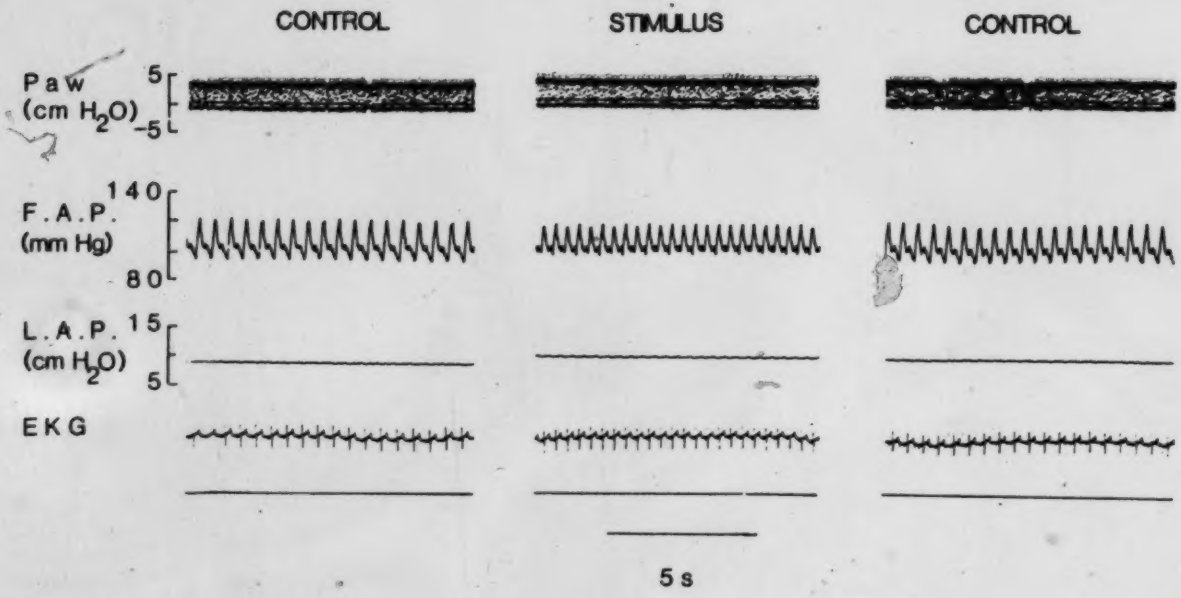

FIGURE 16 HEART RATE RESPONSE DURING HIGH FREQUENCY OSCILLATORY VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations and arrangement as in Figure 15. The heart rates were 108, 142, and 117 beats/min for control, stimulation and final control respectively; there was no significant change with respect to the other parameters.

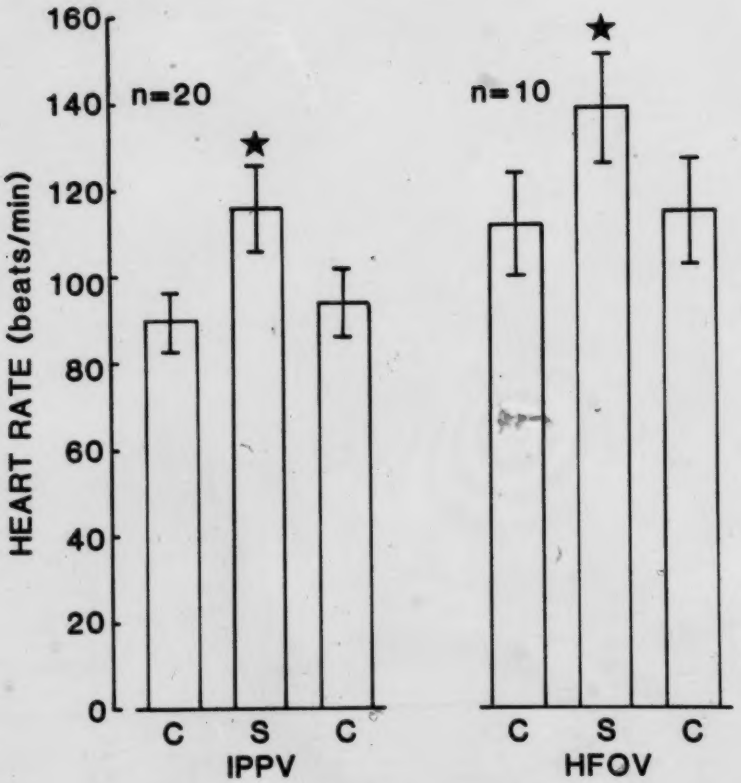

FIGURE 17 HEART RATE RESPONSE DURING INTERMITTENT POSITIVE PRESSURE AND HIGH FREQUENCY OSCILLATORY VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations: (C) control period, (S) stimulation period. Abcissa: sequential stimulations during intermittent positive pressure and high frequency oscillatory ventilation. Ordinate: heart rate (beats/min). The increase in heart rate with each mode of ventilation was significant, but there was no difference among them. The stars (★) indicate statistical significance.

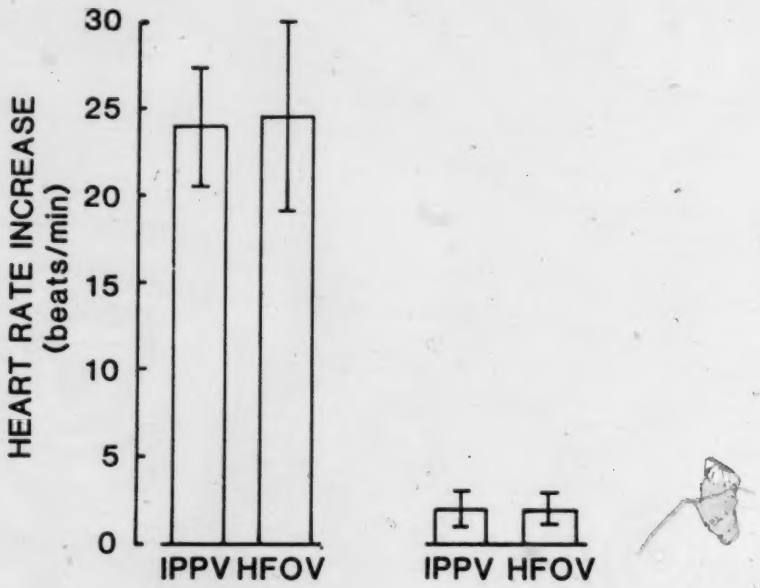

FIGURE 18 HEART RATE RESPONSE WITH LEFT ATRIAL RECEPTOR STIMULATION PRE AND POST ANSA SUBCLAVIAE SECTION: Abbreviations as in Figure 17. Abcissa: sequential results during intermittent positive pressure and high frequency oscillatory ventillation pre and post ansal sectioning; Ordinate: heart rate increase during stimulations. Similar resuts were noted during both modes of ventilation, the heart rate increase following ansal sectioning was not significant.

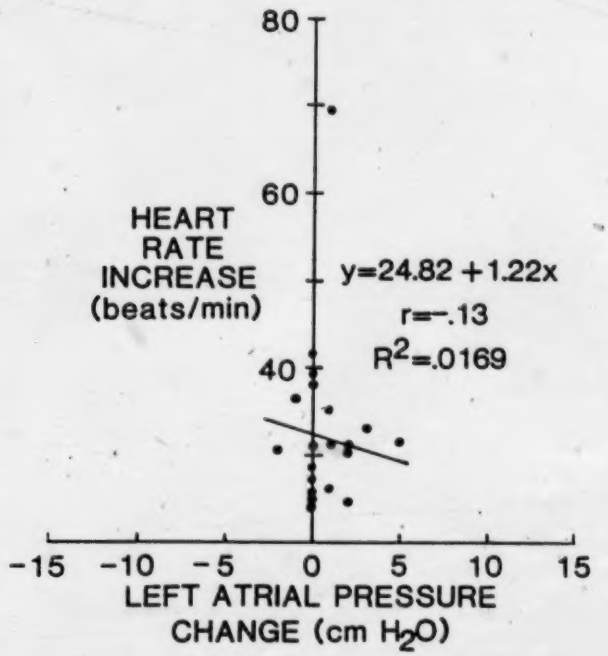

FIGURE 19 HEART RATE INCREASE AND LEFT ATRIAL PRESSURE CHANGE WITH LEFT ATRIAL RECEPTOR STIMULATION: Abcissa: change in left atrial pressure during left atrial receptor stimulation (cm water); Ordinate: heart rate increase (beats/min). Data taken from sequences during intermittent positive pressure ventilation. There was no correlation between the change in left atrial pressure and the heart rate increase. A similar lack of correlation was present during high frequency ventilation.

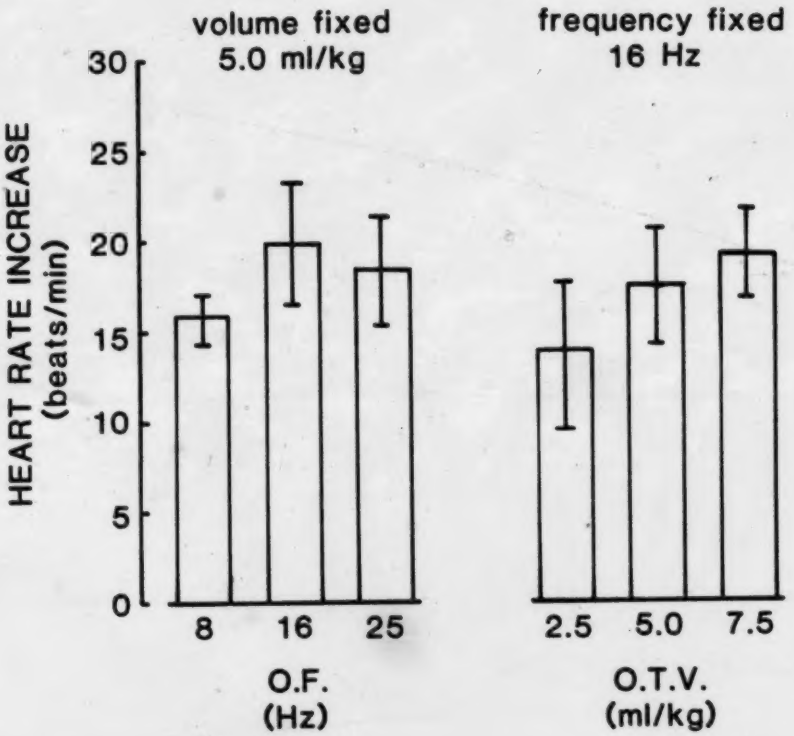

FIGURE 20 HEART RATE RESPONSES WITH LEFT ATRIAL RECEPTOR STIMULATION DURING HIGH FREQUENCY OSCILLATORY VENTIALTION PARAMETER VARIATION: Abcissa: sequential changes in oscillatory frequency and oscillatory tidal volume; Ordinate: heart rate increases during left atrial receptor stimulation. No significant difference in heart rate increase was present during changes in either oscillatory frequency or oscillatory tidal volume.

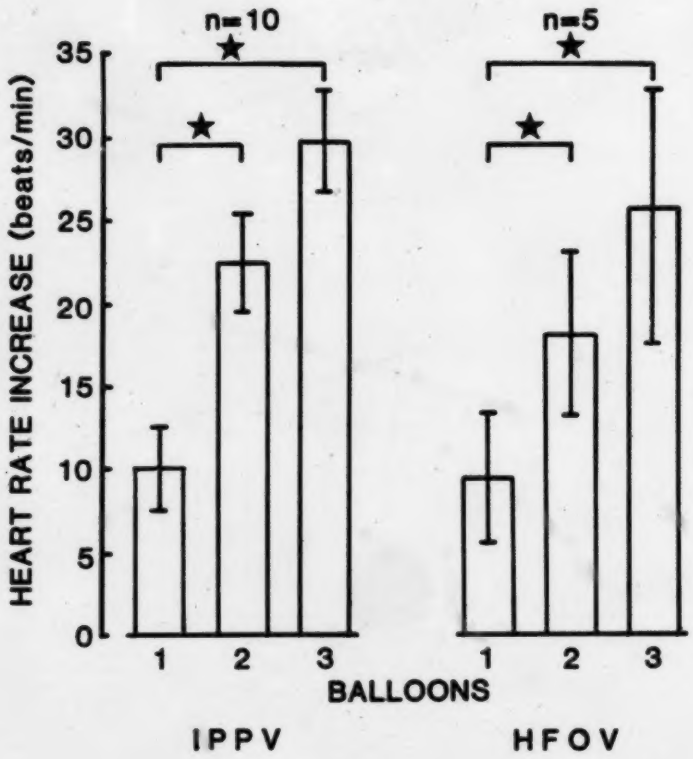

FIGURE 21 HEART RATE RESPONSES WITH GRADED LEFT ATRIAL RECEPTOR STIMULATION: Abcissa: sequential left atrial receptor stimulation with one, two and three sites stimulated during intermittent positive pressure ventilation and high frequency oscillatory ventilation; Ordinate: heart rate increase (beats/min). A significantly greater increase in the heart rate response with either two or three sites stimulated, as compared to one site, was present with both modes of ventilation. Statistical significance is indicated by the stars (★).

FIGURE 22 RENAL RESPONSE DURING INTERMITTENT POSITIVE PRESSURE VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations: (BP) systemic blood pressure, (LAP) left atrial pressure, (Na) sodium, (C) control period, (S) stimulation period. Abcissa: experimental sequence of 10 min.intervals, three intervals for the initial control, three during stimulation, and four post stimulation. For data analysis the first three and and last three were taken as the initial and final contol, the last two intervals during stimulation and the first post was taken as stimulation. Ordinate: six panels are shown for heart rate (beats/min), blood pressure (mm Hg), left atrial pressure (cm water), urine flow (ml/ 10 min segment), osmolarity (mOsm/kg) and urine sodium (mEq/L). During the stimulation period a rise in heart rate, left atrial pressure, urine flow and urine sodium were present, with a drop in osmolarity.

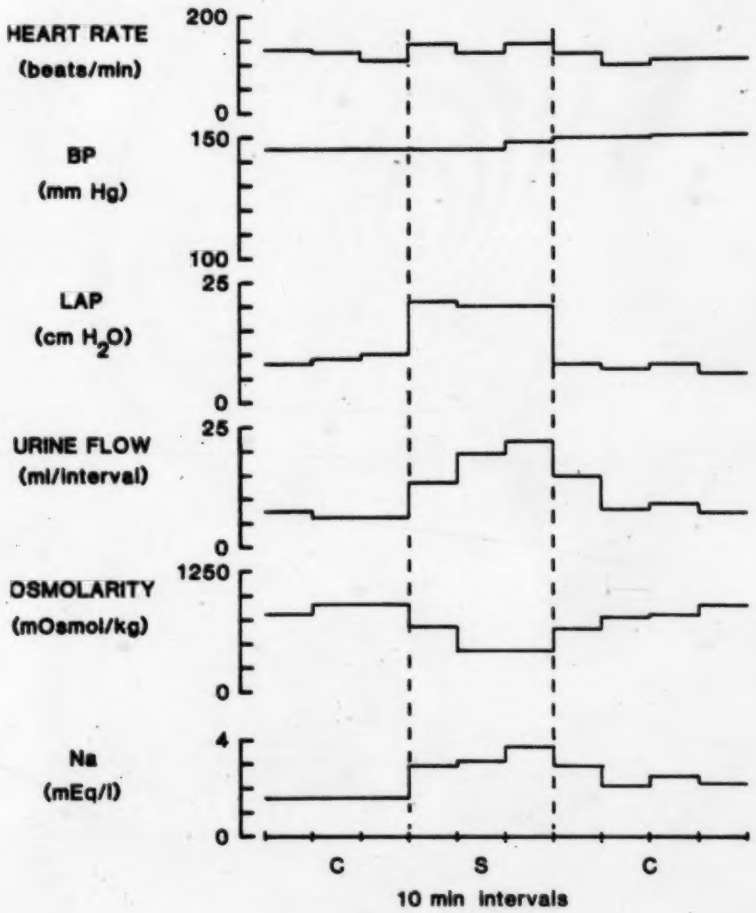

FIGURE 22 RENAL RESPONSE DURING INTERMITTENT POSITIVE PRESSURE VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION

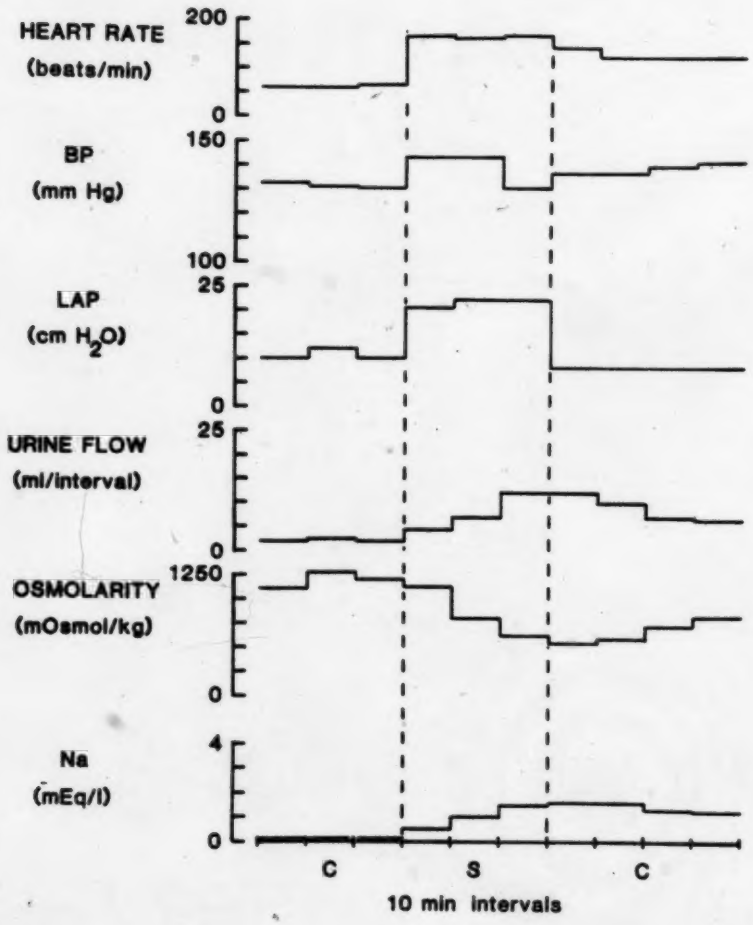

FIGURE 23 RENAL RESPONSE DURING HIGH FREQUENCY OSCILLATORY VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations and arrangements as in Figure 23. The responses were similar to those in Figure 23.

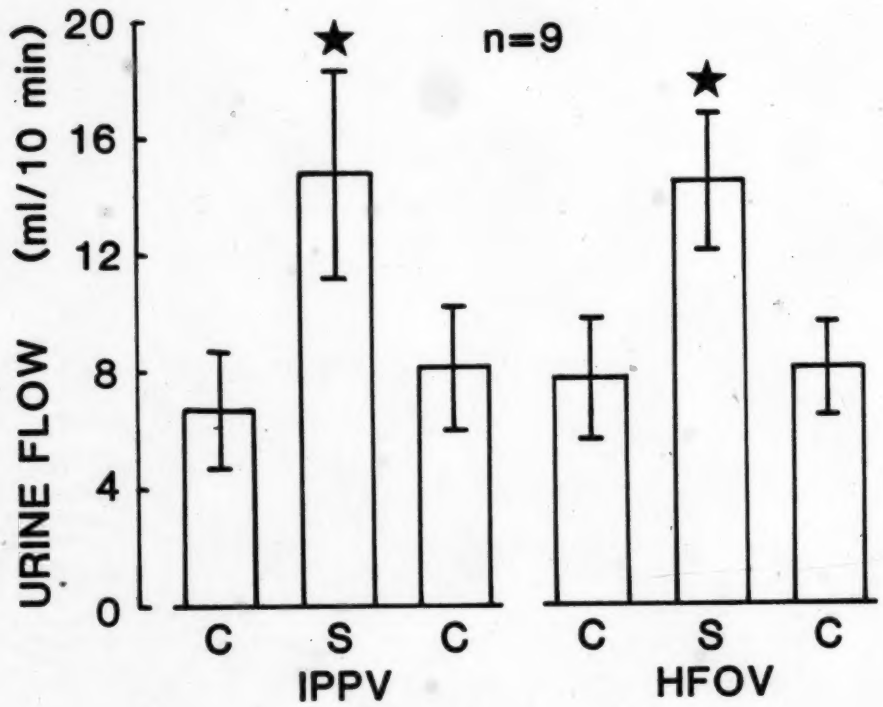

FIGURE 24 RENAL RESPONSE DURING INTERMITTENT POSITIVE PRESSURE AND HIGH FREQUENCY OSCILLATORY VENTILATION WITH LEFT ATRIAL RECEPTOR STIMULATION: Abbreviations: (C) control period, (S) stimulation period. Abcissa: sequential responses during intermittent positive pressure and high frequency oscillatory ventilation. Ordinate: urine flow per 10 min interval (ml). A similar significant increase in urine flow was noted with both modes of ventilation. Statistical significance is indicated by the stars (★).

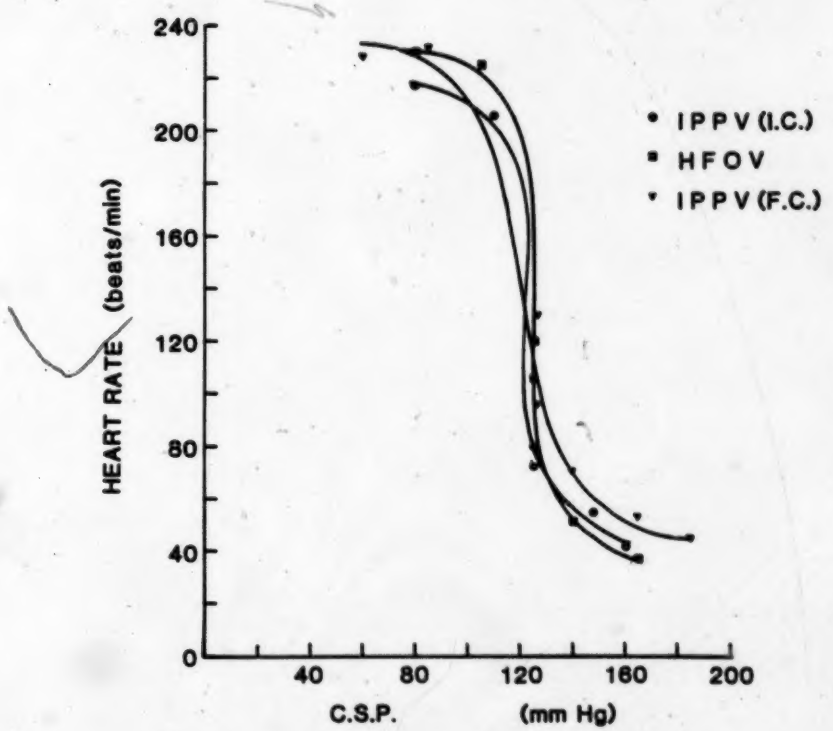

FIGURE 25 HEART RATE RESPONSE WITH ISOLATED CAROTID SINUS STIMULATION: Abbreviations: (C. S. P.) carotid sinus pressure, (IPPV I. C.) intermittent positive pressure ventilation, initial control; (HFOV) high frequency oscillatory ventilation; (IPPV F. C.) intermittent positive pressure ventilation, final control. Abcissa: carotid sinus pressure (mm Hg); Ordinate: heart rate (beats/min). Curves fitted by eye. Data taken from initial intermittent positive pressure ventilation run, the high frequency oscillatory ventilation run and the final control intermittent positive pressure ventilation run. A similarity between the responses was evident.

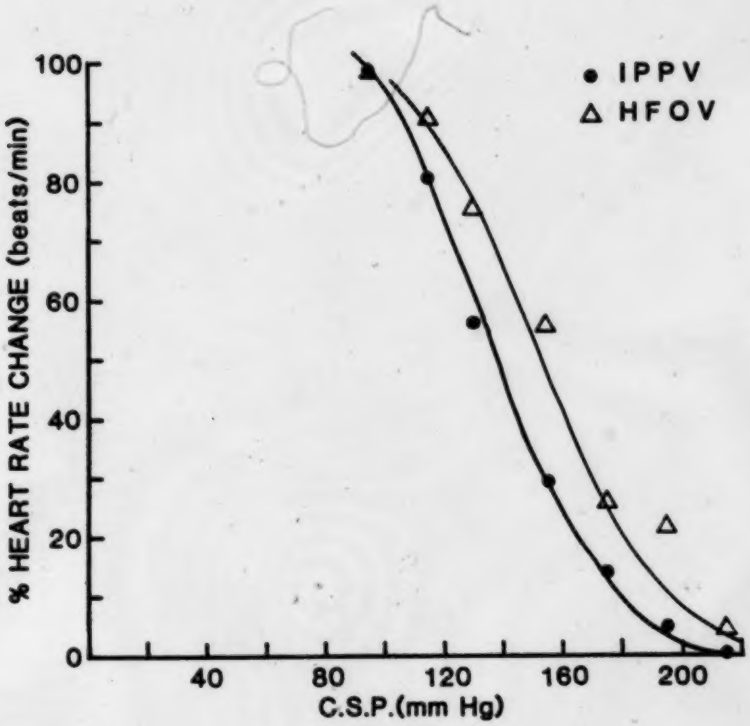

FIGURE 26 HEART RATE RESPONSE WITH ISOLATED CAROTID SINUS STIMULATION: Abcissa: carotid sinus pressure (mm Hg); Ordinate: percent heart rate change (beats/min)[normalized heart rate]. The curves for intermittent positive pressure ventilation (IPPV) and high frequency oscillatory ventilation (HFOV) were fitted by eye. With the method of least squares for slope analysis of the linear section of the curves no difference existed between the two modes of ventilation. The curve for high frequency ventilation was shifted significantly to the right. The values for the percent heart rate change for each setting of the carotid sinus pressure were obtained from repeated runs and then averaged, this resulted in the values obtained during high frequency ventilation not going completely from 0 to 100 percent.

TABLE 1 Physiological Parameters, Protocol 11A.

The values for systemic blood pressure (mm Hg), left atrial pressure (cm water) and mean airway pressure (cm water) during intermittent positive pressure and high frequency oscillatory ventilation pre and post ansa subclaviae sectioning are shown. Significant changes are noted only for left atrial pressure during periods of stimulation prior to ansal sectioning.

TABLE 1 Physiological Parameters, Protocol 11A

	BLOOD PRESSURE (mm Hg)			LEFT ATRIAL PRESSURE (cm H_2O)			AIRWAY PRESSURE (cm H_2O)		
	C	S	C	C	S	C	C	S	C
IPPV	116.7 ± 3.6	117.0 ± 4.2 n=20	114.4 ± 4.1	6.1 ±0.8	7.2 ±0.8 n=20	6.4 ±0.7	4.2 ±0.2	4.5 ±0.3 n=20	4.4 ±0.3
HFOV	121:5 ± 5.6	120.8 ± 4.1 n=10	119.2 ± 4.2	6.0 ±1.0	8.1 ±1.2 n=10	6.1 ±1.0	3.5 ±0.5	3.6 ±0.5 n=10	3.7 ±0.5
POST ANSA CUTTING IPPV	123.8 ± 5.7	120.4 ± 5.8 n=10	117.9 ± 4.2	6.3 ±1.5	6.4 ±1.2 n=10	6.0 ±1.7	4.3 ±0.2	4.2 ±0.2 n=10	4.1 ±0.2
POST ANSA CUTTING HFOV	118.2 ± 7.7	118.2 ± 9.1 n=5	122.6 ± 9.3	10.4 ±3.6	11.4 ±4.2 n=5	9.0 ±5.4	2.8 ±0.9	3.2 ±0.6 n=5	3.2 ±0.6

TABLE 2 Mean Heart Rates, Protocol 11B

Abbreviations: (O. F.) oscillatory frequency, (O. T. V.) oscillatory tidal volume, (C.) control periods, (S.) stimulation periods. Mean heart rate during the various respirator parameters of protocol 11B are given; there is no significant difference between the values.

HEART RATE
(beats/minute)

O.F. (Hz)/O.T.V.(ml/kg)	C	S	C
8/5	96.6 ± 6.0	114.4 ± 5.6	100.0 ± 5.7
16/5	98.9 ±10.8	121.5 ± 9.8	105.4 ±10.0
25/5	112.0 ± 8.9	129.6 ± 6.2	110.0 ± 8.3
16/2.5	83.8 ± 7.1	101.9 ± 9.4	89.5 ± 8.1
16/5.0	90.6 ± 7.1	108.8 ± 8.1	91.6 ± 6.7
16/7.5	100.0 ± 7.2	121.0 ± 7.9	103.8 ± 6.1

All the heart rates during the stimulation periods are significantly greater than during the control periods.

TABLE 3 Physiological Parameters, Protocol 11B

Abbreviations: (B. P.) systemic blood pressure, (L. A. P.) left atrial pressure, (Paw) mean airway pressure, (I. V. C. P.) inferior vena caval pressure, (O. F.) oscillatory frequency, (O. T. V.) oscillatory tidal volume. There is no significant difference among any of the physiological paraneters measured at different respirator settings.

O.F. (Hz)	O.T.V. (ml/kg)	B.P. (mm Hg) n=8			L.A.P. ($cm H_2O$) n=8			Paw ($cm H_2O$) n=8			I.V.C.P. ($cm H_2O$) n=5		
		C	S	C	C	S	C	C	S	C	C	S	C
8/5		121.5 ± 4.4	120.8 ± 3.9	120.4 ± 5.8	8.6 ±0.8	8.3 ±1.0	7.9 ± 0.9	1.6 ±0.4	1.6 ±0.5	1.4 ±0.4	7.4 ±0.9	7.2 ±1.2	7.6 ±1.2
16/5		119.8 ± 6.2	119.5 ± 5.7	119.9 ± 5.6	9.4 ±0.6	9.0 ±0.7	9.0 ± 0.7	2.6 ±0.9	2.8 ±0.6	2.7 ±0.5	9.2 ±0.9	8.8 ±0.7	8.6 ±0.8
25/5		120.8 ± 5.5	120.0 ± 5.1	121.9 ± 5.2	9.1 ±0.8	9.1 ±0.9	8.9 ±10.0	3.5 ±0.4	3.5 ±0.4	3.5 ±0.4	8.4 ±0.9	8.4 ±1.1	8.6 ±1.3
16/2.5		126.0 ± 5.8	125.5 ± 5.3	122.6 ± 4.8	8.9 ±1.0	9.0 ±0.9	9.4 ± 0.6	1.5 ±0.3	1.4 ±0.3	1.5 ±0.3	7.8 ±0.4	7.8 ±0.6	8.0 ±0.6
16/5.0		123.1 ± 5.9	123.5 ± 5.3	123.8 ± 5.5	9.0 ±1.0	9.1 ±1.1	9.0 ± 1.0	2.7 ±0.2	2.8 ±0.2	2.8 ±0.2	8.2 ±0.6	8.4 ±1.1	7.0 ±1.8
16/7.5		127.9 ± 5.8	122.3 ± 4.3	125.1 ± 5.4	9.0 ±0.8	9.1 ±1.0	9.1 ± 0.9	3.9 ±0.5	4.1 ±0.5	4.1 ±0.5	8.8 ±0.5	9.0 ±0.6	8.0 ±1.3

TABLE 3 Physiological Parameters, Protocol 11B

O.T.V. (ml/kg)	O.F. (Hz)	pH	pCO_2 (mm Hg)	pO_2 (mm Hg)
5	16	7.40±.01	32.6±2.3	164.0±18.9
5	8	7.40±.02	34.8±3.4	142.8±23.1
5	25	7.40±.04	37.7±4.5	134.3±10.7
2.5	16	7.34±.02	41.2±3.7	143.0±12.1
7.5	16	7.48±.01	28.1±3.2	153.2± 6.2

TABLE 4 ARTERIAL BLOOD GASES, PROTOCOL 11B: Abbreviations: (O. T. V.) oscillatory tidal volume, (O. F.) oscillatory frequency. The various combinations of high frequency oscillatory ventilation pump parameters are listed in the two columns on the left hand side and the respective arterial blood gases in the three columns on the right hand side. There is no statistically significant difference between any of the values at the different respirator settings but a trend to a respiratory alkalosis at higher oscillatory tidal volumes and a acidocis at lower oscillatory tidal volumes is present.

	BLOOD PRESSURE (mm Hg)			LEFT ATRIAL PRESSURE ($cm H_2O$)			MEAN AIRWAY PRESSURE ($cm H_2O$)		
	C	S	C	C	S	C	C	S	C
3B IPPV	123.5 ± 3.8	120.0 ± 4.2	124.0 ± 4.1	9.9 ±1.0	10.0 ±1.1	10.0 ±1.2	3.4 ±0.1	3.4 ±0.1	3.4 ±0.1
3B HFOV	124.0 ± 5.3	121.4 ± 6.9	123.4 ± 5.6	9.0 ±2.1	8.9 ±2.1	8.7 ±2.0	2.8 ±0.4	2.8 ±0.4	2.8 ±0.4
2B IPPV	124.0 ± 4.1	125.0 ± 4.4	124.5 ± 4.1	10.0 ±1.2	9.7 ±1.3	9.6 ±1.0	3.4 ±0.1	3.5 ±0.2	3.4 ±0.1
2B HFOV	122.4 ± 5.1	125.0 ± 5.7	125.2 ± 4.1	8.7 ±2.0	9.1 ±2.1	8.9 ±2.1	2.8 ±0.4	2.8 ±0.4	2.8 ±0.4
1B IPPV	124.5 ± 4.1	125.5 ± 4.3	125.0 ± 4.2	9.6 ±1.0	9.5 ±1.1	9.6 ±1.0	3.4 ±0.1	3.4 ±0.1	3.4 ±0.1
1B HFOV	123.6 ± 5.0	122.6 ± 5.6	124.0 ± 7.3	9.1 ±1.9	8.7 ±2.0	8.9 ±2.1	2.8 ±0.4	2.8 ±0.4	2.7 ±0.4

IPPV - n=10
HPOV - n=5

TABLE 5 PHYSIOLOGICAL PAPMETERS, PROTOCOL 11C:Abbreviations: (B) balloon. Table arranged as in Table 1. There is no difference between the hemodynamic parameters or airway pressure with any of the varied number of sites of stimulation or with either of intermittent positive pressure or high frequency oscillatory ventilation..

	IPPV			HFOV		
	C	S	C	C	S	C
OSMOLALITY mOsm/kg	940 ±74	621 ±72	804 ±71	853 ±86	567 ±56	799 ±82
		P < .05			P < .05	
NA mEq/10 min	1.59 ±.48	2.57 ±.62	1.84 ±.46	1.69 ±.43	2.72 ±.53	1.81 ±.37
		P < .05			P < .05	
NA mEq/l	212 ±37	201 ±23	228 ±30	196 ±35	168 ±23	206 ±32
		NS			NS	

TABLE 6 URINARY PARAMETERS, PROTOCOL 11D: Abbreviations: (C) control periods, (S) stimulation period. Significant decreases in urinary osmolality and increases in total sodium excretion were present with both intermittent positive pressure and high frequency oscillatory ventilation. No change in urine sodium concentration was recorded.

Carotid Sinus Pressure (mmHg)	Systemic Blood Pressure (mmHg)		Mean Airway Pressure (cm water)	
	IPPV	HFOV	IPPV	HFOV
55	125.0±6.1	122.0±0.0	3.7±0.2	3.3±0.0
75	124.4±4.5	121.2±4.0	3.5±0.2	3.9±0.3
95	121.7±4.4	118.0±3.4	3.5±0.2	3.7±0.5
115	125.3±3.1	123 3±3.1	3.5±0.1	3.7±0.2
135	129.5±3.1	129.4±5.0	3.6±0.2	3.7±0.2
155	129.8±4.1	117.5±2.4	3.7±0.2	3.9±0.6
175	126.4±3.2	124.7±3.0	3.7±0.3	3.7±0.3
195	131.0±2.5	125.0±5.4	3.8±0.2	4.1±0.6
215	131.7±4.8	135.0±0.0	4.3±0.1	4.2±0.0

TABLE 7 PHYSIOLOGICAL PARAMETERS, PROTOCOL III: The values for systemic blood pressure (mm Hg) and for mean airway pressure (cm water) for each step increment of carotid sinus pressure (mm Hg) are shown both during intermittent positive pressure and high frequency oscillatory ventilation. There was no statistically significant difference between values at different carotid sinus pressures or modes of ventilation.

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Publications

Abstracts:

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